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THE TREATMENT OF SYPHILIS

by

ARYLARSONATES.

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by

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THE TREATMENT OF SYPHILIS BY ARYLARSONATES.

INTRODUCTION.

As a result of the recent rapid advances made in almost every department of medical science and especially in pharmacology and experimental therapeutics, the gradual abandonment of empirical for rational therapy, the expression of opinions, some of which were almost revolutionary in character, the introduction of the ultra-microscope, the improved methods employed in the culture and staining of micro-organisms, the improved technique of serum diagnosis and serum treatment, the introduction of the opsonic theory, and the elaboration of both synthetic and biochemistry, it was but natural that scientific men, both at home and abroad, should again have turned their attention towards the elucidation of the real aetiology of Syphilis, a disease said to be almost as old as the human race itself. By common consent, based almost wholly on clinical grounds, this disease had long been included among the granulomata which are definitely known to be of microbial origin, and treated on purely empirical grounds.

On referring to the writings of Hippocrates and Galen, we find no reference whatever made to any such

malady. Passing to the dark and middle ages when superstition was rife, we find many and diverse - and even, as was to be expected, superstitious - views expressed about this malady which by then had fallen as a plague on Continental Europe. With the dawn of bacteriology in the nineteenth century and its rapid advances in the twentieth, scientists began to suspect, from its clinical pictures, and by a comparison with other diseases, that Syphilis was of microbial origin and many observers discovered micro-organisms which were alleged to be the causative factors. Their views, however, almost without exception, were of short duration and soon consigned to the limbo of things forgotten.

In 1884 Lustgarten⁽¹⁾ discovered a bacillus - closely allied and by some said to be identical with the smegma bacillus - which he alleged to be the cause of Syphilis. About ten years later, Van Niessen⁽²⁾ discovered a diphtheroid bacillus which he alleged was the cause of this malady. These two discoveries by these scientists met with some degree of support. In 1902, however, Schüller⁽³⁾ discovered a protozoon which along with the bacilli of Lustgarten and Van Niessen continued to hold the field, until 1905 when Schaudin⁽⁴⁾ and Hoffmann⁽⁴⁾, in somewhat guarded language, announced to the scientific world their epoch-

making discovery, that the disease was caused by a spirochaeta called by them the "Spirochaeta Pallida" on account of its staining properties.

It is now almost generally accepted that the real cause of Syphilis is the protozoon of Schaudin and Hoffmann and this has since been confirmed by other observers as Niesser, Flexner⁽⁵⁾, Uhle, Roux, Mackinney⁽⁶⁾ and Metchnikoff. This then brings us on to the consideration of protozoal diseases.

Besides the bare mention that protozoa are unicellular organisms and belong to an ill-defined group of the animal kingdom of which the amoeba represents the simplest type, and the fact that they are classified as follows:-

- Protozoa
1. Sarcodina with pseudopodia,
 2. Mastigophora with flagella,
 3. Infusoria with Cilia,
 4. Sporozoa with no motile organs,

I do not propose, and it is not within the scope of this thesis, to enter into their life history and sub-classification, etc. All this information can be gathered from special text books on Zoology, Bacteriology and various medical publications. After the brilliant discovery of the late Professor Koch that African Sleeping Sickness - a protozoal disease - was caused by a trypanosoma, and his authority

that Atoxyl (an organic preparation of arsenic and aniline) was a specific for that malady, protozoal diseases assumed great importance from their therapeutic aspect. Bacterial and protozoal diseases differ in these essentials:-

- (a) The former (e.g. tuberculosis) are caused by infection from the vegetable, while the latter (e.g. malaria, syphilis) are caused from the animal world.
- (b) The former nearly always undergo the whole phase of their evolution or life history in one host while the latter, almost without any exception, require more than one host.

Many are the points of similarity and dissimilarity between protozoal and bacterial diseases.

In some bacterial diseases where the causative micro-organisms can be cultivated in vitro, the corresponding rational therapy resolves itself into the administration or introduction of anti-bodies in various definite amounts into the body of the host with a view to destroying or otherwise preventing the action of the germs themselves or the baneful bodies eliminated or produced during the growth and evolution of the bacteria.

In protozoal diseases, where the causative organisms pass their life cycle through several hosts, it

is difficult, if not wholly impossible, to cultivate the micro-organisms in vitro and hence the difficulty of preparing antibodies to neutralize the morbid substances produced during that period of their life cycle in man, the host in which, as physicians, we are interested.

It would suit my purpose to briefly consider specifics which are drugs, bodies or remedies which have specific or infallible actions or power in particular diseases. As examples of them, I may mention mercury in Syphilis, and quinine in Malaria.

When mercury is administered in Syphilis, it is said to gain entrance to the special cells of the syphilitic lesions and cause a separation of their nuclei. The cells then undergo fatty degeneration and are absorbed.

In Malaria, if quinine be administered in adequate doses and in time to be absorbed and exert its specific therapeutic action just before the Zygoblasts of the Malarial plasmodium are floating free in the blood plasma (i.e. after they have been extruded from the erythrocytes) it causes their rapid destruction and elimination.

Some specifics are "rational", others "empirical". Many and diverse opinions have been expressed as to the specificity of the arylarsonates in Protozoal

diseases. In some forms of protozoal diseases, e.g. sleeping sickness (as mentioned above), Atoxyl, an arylarsonate, brings about, according to some authorities, a permanent cure, e.g. when animals with trypanosomes in the blood are injected with Atoxyl (mono-sodium-para-amido-phenyl-arsonate) the trypanosomes disappear, although the blood is still infectious. If both Atoxyl and Mercury are injected, the trypanosomes are entirely destroyed. If the same experiments are carried out in patients suffering from trypanosomiasis, Atoxyl alone is found sufficient to destroy the trypanosomes.

Applying the argument that trypanosomes and spirochaetae are morphologically related to each other, it is but natural that remedies found beneficial in trypanosomiasis should be tried in cases of spirochaetal infection.

In Syphilis (a chronic spirochaetosis) it is found by experiment that Atoxyl treatment causes the rapid disappearance of chancres, gummata and skin eruptions when injected in their immediate vicinity. Certain other syphilitic lesions (e.g. visceral syphilis and meta-syphilitic affections), however, are said to remain unchanged. Arsenic (and Atoxyl is an arsenical preparation) therefore in suitable forms is of considerable therapeutic value and is useful where

mercury and iodides are making little or no progress or, for various reasons, are badly tolerated. Besides atoxyl, other arsenical preparations, e.g. Orsudan, Soamin, Arsacetin, Arseno-phenyl-glycin, Atoxylate of Mercury, Dioxy-diamino-arseno-benzol, etc. have been experimentally used for the same purpose.

I may here quote some of the conclusions of Professor Hallopeau in the use of Atoxyl and in the chapter on the history of the Arylarsonate treatment, I shall deal very fully with the various views expressed by various people on the subject. According to him, then, "It would very probably be possible to "cure Syphilis by injections of Atoxyl if it were "possible to repeat them for a long enough period at "sufficient doses. Unfortunately this is not possible and the injections have to be stopped after a "varying number have been given owing to symptoms "indicating intolerance."

Among the diseases now definitely known to be protozoal are the following:- Sleeping Sickness, Dourine, Nagana, all due to trypanosomes; Malaria to the Plasmodium malariae, a protozoon or haematozoon; Kala-azar to the Leishmania Donovanii; Syphilis to the Treponema Pallidum; Yaws to the Treponema Pertenuis; Relapsing Fever to the Spirillum Obermeieri.

Besides these the reported good results of arsenical treatment in Pellagra, Pernicious Anaemia and certain skin diseases raises the question of the protozoal origin of these.

Passing now to the therapeutic aspects of morbid conditions in which we, as physicians, are concerned, it immediately occurs to us that there must be some essential difference between the action of trypanocidal drugs "in vitro" and "in corpore". Bearing in mind what has already been said, that it is difficult, if not wholly impossible, to cultivate protozoa in artificial media "in vitro" on account of their passing their life history through more than one host, we find that even in cases where their life history has been fully worked out, e.g. the plasmodium malariae, we have got no nearer to any rational mode of treatment since vaccine therapy is only possible in some cases where the organisms can be cultivated in vitro. There is thus little cause for wonder that the remedies tried in protozoal diseases have been legion and are almost wholly empirical.

In the administration of a drug to combat a bacterial infection, we must consider

- (a) The effect of the remedy upon the host and
- (b) Its effect on the invading or infective micro-organisms.

We must then exhibit the drug in quantities that will be destructive to the micro-organisms or their products or both, and at the same time innoxious to the host, e.g. when Quinine is exhibited in Malaria - a microbial or protozal disease - it causes in moderate doses, administered at the proper time, a total disappearance of the plasmodium from the Erythrocytes. If given in large doses, it also acts on the host, causing in man the following:-

(a) A decrease or even cessation in the amoeboid movements of the leucocytes.

(b) A specific baneful action on some of the organs of sense (e.g. that of hearing) and on some portions of the nervous system.

(c) Certain cutaneous eruptions.

If it were possible to cultivate protozoa in vitro we would then establish a rational therapeutic basis and by repeated experiments on animals, and even on man, we would no doubt be able to determine what dose of the specific to exhibit and I have little doubt that it would assume the form of some antibody or vaccine!

The scope of my thesis is the following:-

(1) To give an outline of the history of the subject and its position at the present time.

(2) To compare the results of different Arylarsonates, and show whether they hold out promise of becoming established therapeutic agents.

(3) To give the results of trial in a series of cases of the various Arylarsonates paying special attention to the action of the preparation in bringing about a permanent cure as proved by the absence of the Wassermann ⁽⁷⁾ reaction after treatment.

I may mention that the apparatus I use for testing the Wassermann reaction in cases of Syphilis treated by me and in other diseases where I suspected a syphilitic taint, is the Syphilis Diagnosticum outfit.

HISTORICAL OUTLINE.

Recent research by Ehrlich and others has concerned itself with the investigation of various chemical compounds which by their action on the parasites or toxines within the body either cause destruction or neutralization of the morbid agent and so cure the disease. In this section of my thesis I propose to give an account in chronological order of the introduction of the most important arylarsonates which have been used in the treatment of Syphilis which in the light of modern medical research has been already justly described as a chronic spirochaetosis or spirillosis. In the chapter on the Chemistry of the Arylarsonates, I shall define this term. The arylarsonates which I shall bring before your notice are Atoxyl, Soamin, Arsacetin, Arsenophenyl-glycin, Mercury Atoxylate and the newest and most important preparation of all, viz: Dioxy-diamino-arseno-benzol, also known as Ehrlich-Hata preparation No.606. (Salvarsan).

Mercury in various forms has for a long time been used empirically in the treatment of Syphilis and the medical profession has long since recognised that there are instances, some of which can be explained only on the hypothesis of an idiosyncrasy, and others where definite renal and hepatic lesions exist, that mercury, even aided by other drugs like

the iodides, had little, if any, action on the disease or could not be administered with impunity. In some cases lesions either known to be syphilitic or to have a close relation to this disease (e.g. para- or meta-syphilitic lesions) were found to be refractory to the use of mercury in any known form — perhaps owing to the treponema in its life history in man assuming a form unaffected by mercurials. It is not surprising then that medical men began to try other remedies in order to discover, if possible, some substitute for mercury. It was observed that Arsenium both in its physical properties and its chemical compounds bore a strong resemblance to Mercury. It was also discovered by experimental pharmacology that it (arsenic) could be exhibited in very much larger doses when in an organic form than was formerly possible in the inorganic compounds that were used.

The first arylarsonate which I shall bring to your notice is Sodium-amino-phenylarsonate also called ATOXYL (a registered trade name) which was first prepared over fifty years ago by the French Chemist Bechamp and which was introduced into medicine about ten or twelve years ago.

In laboratory experiments, Thomas & Breinl⁽¹⁾ found that it had a marked trypanocidal action and naturally suggested that it should be used in Sleeping

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Sickness, a disease then known to be of protozoal aetiology from the researches of Castellani, Bruce, Nabarro and Low. The Liverpool School of Tropical Medicine then formally introduced this drug in the treatment of Sleeping Sickness and its subsequent use by Koch on a large scale in Sleeping Sickness in Uganda proved its undoubted therapeutic efficacy. In 1905 came Schaudin & Hoffmann's ⁽²⁾ epoch-making discovery of the protozoal nature of Syphilis and the subsequent classification from morphological and other grounds of the protozoon as a Treponema. Proceeding, then, on rational lines, it was but natural that a remedy which had proved its efficiency in one protozoal disease should be given a trial in another, viz. Syphilis. The results were marvellous and workers on the Continent vied with one another in publishing the results of their experiments. As far as I am aware, Atoxyl was first used in the treatment of Syphilis at the Institut Pasteur, and the results obtained there when first published were received with much scepticism. I cannot do better than to summarise the statements made and views expressed by eminent authorities when the publications of the Atoxyl treatment were first received. P. Meissner ⁽³⁾ said that so favourable were the reports received from France of the use of Atoxyl in the treatment of Syphilis

that some ascribed them to the natural enthusiasm for exaggeration existing among Frenchmen. The reports were first received with scepticism, but when different investigators in other lands reported similar results we could not help but believe them and recognise the fact that a new era in the treatment of Syphilis had dawned.

In "Arsenic bei der Syphilis-Behandlung", the epoch-making work of Paul Salmon⁽⁴⁾ he said that he had treated a certain number of syphilitic patient with arsenic alone and had obtained most encouraging results, that Atoxyl had a favourable influence for certain trypanosomal and spirillar diseases, and that from that time arsenic could be reckoned a specific in Syphilis. He found the remedial action evident three days after a single injection of .5 gramme ($7\frac{1}{2}$ grains) of Atoxyl and that in less than two weeks the curative process was complete with a rapidity at least equal to that of mercury, and that the general and local atoxicity of Atoxyl gave it great advantages over Mercury and Iodide of Potassium. He observed in none of his cases any intolerance to three grammes of Atoxyl in one week. The same author in another article⁽⁵⁾ came to the conclusion that Atoxyl could be distinguished by:-

- (a) The certainty of its results,

(b) The rapidity of its action,

(c) The rapid healing of the different forms of the disease.

Other investigators in other countries reported that it was useless, and abandoned it until the appearance of Salmon's epoch-making work (already mentioned above) rekindled their enthusiasm.

At a meeting of the "Berliner Medizinischen Gesellschaft" on February 13th, 1907, and in No.16 of the Berliner Klinischen Wochenschrift, 22nd April 1907, Professor Lassar's attitude was to the effect that Atoxyl was useless against Syphilis.

Shortly after (May 1907) in his lecture on "Atoxyl in Syphilis" before the Berlin Medical Society, he, as a result of the researches of Salmon, Hollochau and Metchnikoff, began to alter his opinions on the use of this drug in Syphilis. He said that he had observed no ill effects, that the quantity of the drug had nothing to do with its effects which were due to the fate encountered by the drug in the organism — depending probably on the greater or lesser alkalinity of the blood. He found that a 10% sterilised solution thrice weekly was enough to produce a retrogression of the symptoms whether it was a recent or chronic case, and that when the drug was injected in the gluteal regions, it had the same effect on primary

sores as corrosive sublimate injections. He observed an abatement of all the symptoms, (a retrogressive metamorphosis) that Atoxyl behaved like mercury, and he hailed the drug as another specific. He hoped that the medical profession would recognise that Atoxyl was of paramount importance and would investigate, as he then was doing, its action on diseases of the central nervous system that had until that time resisted Mercury and the Iodides. At the same meeting of the Berlin Medical Society, and in the paper "Untersuchungen über die Wirkung des Atoxyls auf die Syphilis" further reports on the use of Atoxyl were recorded by P. Uhlenhuth, E. Hoffmann, and K. Roscher.⁽⁶⁾

Two eminent syphilillogists working under the direction of Professor Dr Lesser reported that the drug was particularly useful in Syphilis ulcerosa praecox (malignant Syphilis) and Hoffmann endorses this view.

In his work "Sur le traitement de la Syphilis par l'anilarsinate de soude suivant la procédé de M. Paul Salmon". Professor Hallopeau⁽⁷⁾ confirmed the opinions of the former author, and noted cases of intolerance of the drug. He advised us not to abandon the drug on account of these incidents, that toxic effects were observed when other drugs as Opium, Chloroform, Mercury, Digitalis and Cocaine were first used, that these latter drugs were not set aside

because accidents sometimes occurred with them, that it had a favourable influence on Syphilis and that the symptoms of intolerance were of secondary importance.

On June 10th, 1907, Professor E. Lesser in the course of an address to the "Verein für innere Medizin" on "The treatment of Syphilis in the light of the latest results of Research" said that in every case the symptoms rapidly disappeared, the results obtained were excellent, malignant syphilitic ulceration healed rapidly, that especially in galloping Syphilis it appeared to be equal to calomel injections in its results, and that it was the best method of treatment hitherto known.

In the "Naturwissenschaftlich-medizinischen Gesellschaft zu Jena" at a meeting held on June 20th, 1907, Spiethoff⁽⁸⁾ gave a "Report on the present position of Syphilis investigation" in which he said that with intra-muscular injections all lesions in the primary and secondary stages of the disease and even gummata rapidly disappeared.

Dr Felix Moses⁽⁹⁾ in a paper "Der heutige Stand der Atoxyl-behandlung der Syphilis" recommended its use where treatment was necessary and Mercury could not be used.

Dr A. Darier⁽¹⁰⁾ in an interesting paper "De l'atoxyl dans la Syphilis oculaire" said that syphilitic

iritis improved rapidly under its use and held out promises of being completely cured. Numerous others as Rouvière⁽¹¹⁾, Krauss & Scherber⁽¹²⁾ also report favourably on the Atoxyl treatment.

The investigations of Neisser⁽¹³⁾ have an extensive bearing upon the whole subject. He said that the reports which were published showed the healing of existing symptoms, but nothing was expressed as to whether a complete destruction of the virus present in the body took place in order to exclude any recurrence of the symptoms. He had made experiments on animals and was able to affirm that if the Atoxyl treatment was energetically prosecuted (large single doses being most effective) it had a most powerful influence on the disease, that the experiments were not aimed at ameliorating the symptoms but to ascertain whether the virus was killed, that while inoculation from the organs (spleen, bone-marrow, etc.) of animals in which the disease was left to itself or treated with various other drugs almost invariably led to positive infection, inoculation after Atoxyl treatment almost invariably gave negative results, and that he had not yet ascertained whether a complete sterilisation of the animals was attained or only such a degree of annihilation that the remaining traces escaped transmission by the organ inoculation.

All I have quoted, then, prove beyond doubt that Atoxyl exercises an actual specific action on Syphilis.

Besides its use as a curative agent, it possesses properties which, when exhibited in proper doses and at definite ascertained periods, are said to prevent the appearance of syphilitic symptoms after inoculation.

Hoffmann, Uhlenhuth and others made experiments on rabbits and concluded that its effects were not only healing, but also preventitive, and that the utilisation of these results would appear to be indicated for human syphilitic pathology.

In September 1907, Metchnikoff related to the audience at the International Congress of Hygiene at Berlin the results of experiments he had conducted on anthropoid apes with Atoxyl as a prophylaxis in Syphilis.

He recorded two sets of experiments controlled by other monkeys to which no Atoxyl was administered.

In the first set of experiments he exhibited Atoxyl subcutaneously at intervals of a few days after inoculation with the specific virus, and no symptoms appeared.

In the second set of experiments, he injected one dose a long time - about fifteen days - after inoculation and no syphilitic symptoms also appeared. As

the result of these experiments, he concluded that besides a healing action on already existing syphilitic symptoms, Atoxyl also possessed a prophylactic action.

Wassermann⁽¹⁴⁾ used it in meta- or para-syphilitic lesions, and, as was to be expected, it had no effect upon already formed organic lesions of the central nervous system. Some authorities, however, consider that it holds out good prospects as a prophylaxis even in these lesions. As is customary after the appearance of a new remedy and the zeal of early experimentists, certain alarming symptoms did occur. They were mostly of the nature of arsenical poisoning with all its usual signs. These toxic symptoms seemed to affect principally the eyes and many cases of blindness occurred.

Von Graefe's⁽¹⁵⁾, in his memoir, treats of the action of Atoxyl on the visual apparatus at great length and gives an account of thirty-seven cases including most of those given in the tables in Bulletin No.8, p.308, and some others. Igersheimer and Paderstein do not differ very much in their descriptions of the onset and course of Atoxyl amblyopia. They regard the prognosis as unfavourable and therapy as powerless. Igersheimer experimented on different animals to which he had given Atoxyl in various ways,

and cut sections of the nerve apparatus of the eye. As the result of these experiments, he came to the conclusion that Atoxyl had a selective action on the nerve cells of the organ of vision without setting up reactive processes in the neighbourhood of the degenerative focus, that the point of attack of the poison may be central, peripheral, or, in the course of the optic nerve, that often the substance seemed to be fixed (verankert) at several points at once and to evoke simultaneous morbid processes. He said that in arsenical poisoning, affections of the optic nerve were rare while the prognosis was good, that rarer still were the affections of vision attributable to aniline the prognosis of which was again favourable, and that one was compelled to think that the specific action of Atoxyl was independent of its arsenic or aniline components. He compared in various animals the symptoms and post-mortem lesions of poisoning by aniline and arsenic on the one hand and Atoxyl on the other, pointed out that renal haemorrhages almost always occurred in Atoxyl poisoning of the dog, but very rarely after poisoning by arsenic, that in the bulb of the dog and cat after several days' treatment with Atoxyl arsenic was found, but after the administration of the equivalent quantity of sodium arsenate none was found. The following is a summary of some of

Igersheimer's conclusions.

(1) Atoxyl amblyopia in man in most cases occurs under the form of a simple progressive optic atrophy in which pallor of the papilla may occur very early or very late. Quite exceptionally (Fehr's cases) the amblyopia is stationary and in the form of a retrobulbar neuritis.

(2) Extreme changes purely of a parenchymatous nature are found in the optic nerve fibres near the chiasma in post-mortem examinations in men.

(3) There was nerve degeneration in the eyes of rabbits when small and moderate quantities of Atoxyl were introduced under the conjunctiva or into the vitreous humour.

(4) There occurred degenerative processes in the inner layers of the retina and in the optic nerve in dogs and cats when Atoxyl was administered subcutaneously.

(5) Cats became very nervous after Atoxyl, and after death marked changes were seen in the cells of the brain and spinal cord with special localization in the optic thalamus.

(6) In man atoxyl amblyopia had a different clinical course from that caused by arsenic and aniline.

(7) Chemical examination showed that very strong affinity exists in the bulb for the atoxyl molecule but not for inorganic arsenic.

(8) These changes are independent of affections of the internal organs.

(16)

Mr Ernest Clark also has had several cases of optic atrophy to record after the use of atoxyl.

It was early recognised that the exact chemical composition of Atoxyl (according to the source of its manufacture) was subject to great variation, and that different preparations of the same drug had different therapeutic effects. The amount of arsenic in it was found to be inconstant depending on its mode of preparation and the amount of water of crystallisation it contained. Some of the early preparation (especially the German ones) were very toxic and gave rise to severe cases of poisoning. The exact chemical nature of the drug then became the subject of investigation and an extensive series of researches on the arylarsonates were commenced by Messrs Burroughs Wellcome & Co. in 1907. The result of these experiments was the introduction into therapeutics of

Orsudan and Soamin which differ little (apart from chemical composition, water of crystallisation, solubility, and amount of arsenic present) from each other.

SOAMIN, then, is the arylarsonate I propose to deal with next. It is a registered trade name and a pure and stable form of Sodium-para-amino-phenylarsonate. After numerous experiments by competent observers, this drug has not been found wanting and the results obtained with it have been very striking. The first published report of its use occurred in the Journal of the Royal Army Medical Corps of April 1908 and referred to thirty cases, some of which were of great severity. To obtain an accurate idea of its therapeutic value it was exhibited only in those cases where the diagnosis of Syphilis was established (by every available means) beyond a doubt. The writer of the article referred especially to the absence of any symptoms of intolerance or toxicity after its use and said that in no single case did the patient complain of any symptoms which could be attributed to the drug. Its beneficial action seemed to be most marked in those cases where there was ulceration of the mucosa of the mouth, tongue or throat. In five of the thirty cases recorded here a very marked change in the condition was noticed even after the second injection, by which time the ulcers had assumed a much cleaner

condition. In one week dirty foul ulcers healed up. Its action was well marked in one severe case in this category. From a study of these thirty cases, we find that Soamin causes a complete disappearance of the symptoms of the disease. With reference to its power to effect a permanent cure, the author said it was yet too early to know how many injections were necessary to stamp out the disease, that a considerable amount of work remained yet to be done in connection with the treatment, that in Soamin we had a very valuable agent in the treatment of Syphilis, that its action on the lesions of early Syphilis appeared to be equal to, if not better than that of mercury, that it had many advantages over Mercury without any disadvantages, that it was very easily injected and dissolved readily in hot distilled water, its injection was absolutely painless, there was not yet a single complaint of pain or tenderness after injection nor the least suspicion of induration or thickening, its injection was not followed by salivation or spongy gums (so frequent a complication with Mercury), and that in India and other tropical countries when the patients, already debilitated by disease or climatic conditions, were unable to take Mercury in any form, it was of special value because it had a tonic and alterative action.

In the British Medical Journal of August 15th, 1908, pp.391-4, Colonel F. T. Lambkin, R.A.M.C. gave a record of thirty cases treated by him between March 1st, 1908, and July 1st, 1908. In these cases he used Soamin alone and said that during that time he had not seen a single sign of any toxic effect of the drug although the dose (injected intramuscularly) had been considerably increased. He drew attention to its beneficial effects in secondary lues and noticed that since its introduction, ulcerated throats became very rare. In all these cases the drug had a good effect on the general health and all the patients gained weight. In the Lancet of December 5th, 1908, he gave a further detailed account of thirty-four cases of Syphilis which were treated by him at the Military Hospital at Rochester Row. Again, in these cases, its value is fully borne out and its relative non-toxicity as compared with Atoxyl, arsenic acid and inorganic arsenical salts well marked.

In the Medical Press and Circular (November 4th, 1908, pp.494-5) G. Pugin Meldon reported favourably on its uses and said that he believed that a few weeks of Soamin treatment gave one a better chance of warding off the disease than a short mercurial course. In the same paper of November 14th, 1908, Dr Robert Robertson stated that he obtained very

good results with it in a case of Syphilis of long duration in a married woman. In the Lancet, December 26th, 1908, are recorded very rapid healing of malignant tertiary ulcers after four injections of it. In the British Medical Journal of December 12th, 1908, p.1788, we find recorded the rapid healing of intractable specific ulcers and in this same paper of August 28th, 1909, we read of cases demonstrating its value in long standing cases of tertiary Syphilis where Mercury had no appreciable effect. E. U. Bartholomew⁽¹⁷⁾, Benjamin Moore⁽¹⁸⁾, and Lambkin⁽¹⁹⁾, all confirm these reports of the beneficial influence of Soamin.

The toxic effect (denied by some) on the eye has been very rarely observed and perhaps this is due to the fact that it has not been as extensively used as Atoxyl.

I now pass to ARSACETIN, an acetylated form of arsenilate of Sodium, introduced by Ehrlich, and the production of which is one of the triumphs of synthetic chemistry. Those who have used it say that it is remarkable for its low toxicity, good keeping qualities and the sterilability of its solutions.

Ehrlich⁽²⁰⁾, Browning⁽²¹⁾ and Salmon⁽²²⁾ have used it extensively and found that it is for many species of animals three times less toxic and in the

maximum four or five times less than the arsenilate (Atoxyl). Neisser and Salmon found that in monkeys - which of all animals used in the experiments show the greatest affinity to man - that no bad results followed its use, and that an ape of two kilos (body weight) was able to tolerate, and be in good health, as much as fourteen grains of it in four doses within ten days. Experiments made by Ehrlich and Browning with animals (mice) infected with trypanosomiasis have proved that even the severest case which otherwise would result in death within a few hours can be treated successfully with arsacetin, whereas Atoxyl, even in very slight infection had hardly any effect. Experiments on various other species of infected animals (trypanosomiasis as well as other protozoal diseases) have given excellent results throughout so that the introduction of this product into therapeutics as a method of treatment for the human being seemed rational and fully justified, if any importance at all can be attached to experiments on animals. Professor A. Neisser⁽²³⁾ gave the results of the employment of Arsacetin (Ehrlich) in the treatment of Syphilis to the effect that by means of experimental research we had reliable knowledge of the activity of Mercury and also that besides Mercury other specific remedies existed, that he would report on a new arsenical pre-

paration (arsacetin), that the experiments on animals carried out by Uhlenhuth, Metchnikoff and his staff proved with absolute certainty that there were arsenical preparations which were able to destroy completely the syphilitic virus in the body without harm to the animal, that besides the older Atoxyl, we had a new preparation arsacetin prepared by Ehrlich and extensively tried by himself during his stay at Batavia, that the preparation was introduced to meet the desire for a less toxic but equally active preparation as Atoxyl, that compared with Atoxyl, its solutions were very stable at high temperatures, and it could even be heated in autoclaves to 130°C. without suffering decomposition and liberation of arsenic, that the preparation was certainly less toxic than Atoxyl, its remedial action on Syphilis was at least equal to that of Atoxyl, its solution could be stored for long periods without undergoing decomposition, he could recommend it as a very useful preparation, that to judge the efficacy of a syphilitic remedy from its symptomatic relieving action was wholly false if the proof had already been furnished in indisputable fashion — by experiments on animals —, that the drug possessed a reliable curative, virus-destroying action, that they had not observed a single case of optic atrophy or of similar damage to the nervous system, that no renal

disturbances had been observed, passing pain in the stomach and intestines sometimes occurred, and that although men with healthy organs tolerated Arsacetin well, it appeared that already diseases or enfeebled organs were more susceptible to the toxic action.

Colonel Lambkin⁽²⁴⁾ confirmed Neisser's results and in his paper⁽²⁵⁾ "The Arylarsonate treatment of Syphilis; its possible future effects on the services" he spoke very highly of the results he had obtained with it. He said that at present our knowledge of the power of these salts of arsenic over Syphilis was in a very elementary stage, but he looked forward to future experience and improved technique leading us to that goal in the treatment of Syphilis which had already been attained with dourine. The same author⁽²⁶⁾ said that he had tried the drug in a large number of cases and had found it beneficial in primary lesions as well as in cutaneous Syphilides and those of the mucous membranes. It is important to note that Professor Neisser⁽²⁷⁾ said that it would be a mistake - except in cases where Mercury was not tolerated at all, or its action failed (Mercury-resistant Spirochaetes ?) - to abandon Mercury with its established action, for Acetatoxyl (= Arsacetin) the therapeutic value of which, in human Syphilis, was not yet sufficiently known, and that he would for the

present combine both drugs, either employing them simultaneously or successively.

The next Arylarsonate which I pass on to discuss is ARSENO-PHENYL-GLYCIN (in vacuo) also called Spirarsyl and said to be the active reduction product of Atoxyl. Ehrlich introduced it after he and his assistants had carried out very extensive pharmacological tests with it at the Speyer House in Frankfurt-on-Main. H. Wendelstadt⁽²⁸⁾, Ch. Schilling⁽²⁹⁾ and others found it of great value in certain forms of trypanosomiasis and in Syphilis. Alt⁽³⁰⁾ found that it relieved patients who had Epilepsy and Paralysis due to Syphilis, that it was capable of converting a positive Wassermann reaction into a negative one, and that it had no effect whatever on idiotic children with hereditary Syphilis. He noted no secondary action, no optic nerve injury, no albumen and no sugar in the urine after its use, but an increase in body weight and general improvement in every case. Lambkin⁽³¹⁾ on August 14th, 1908, said that there was not yet sufficient time to allow one to express any definite opinion regarding its use, that the fact of it being supplied in vacuo and the dangers attached to it on its exposure to air appeared to him to put it out of count for anything like general use, more especially as the little glass tubes in which it was

supplied were very apt to get cracked in transit, thus exposing the salt to the air.

Neisser⁽³²⁾ in 1908 said that for the present he would always combine both drugs (Arylarsonate and Mercury) either employing them simultaneously or successively.

In the same year that this drug was introduced we find mentioned the introduction of MERCURY ATOXYLATE or MERCURY PARAMIDO-PHENYL-ARSINATE in the treatment of human Syphilis by Uhlenhuth and Manteufel⁽³³⁾ who assumed that the combination of Atoxyl with Mercury would be sure to prove useful in this disease. They first ascertained that the new preparation was efficacious for spirillosis in fowls, Syphilis in rabbits, Spirochaetae of experimental recurrent infection, and trypanosomiasis, and that it possessed a specially destructive action on Spirochaetae. Though scarcely soluble in water it has been shown by experiments in vitro to differ from Atoxyl principally in that it energetically destroys trypanosomes and spirochaetae. Blumenthal⁽³⁴⁾ in his experiments seems to have shown that Mercury Atoxylate (at all events the preparation he employed) was more toxic than Atoxyl owing to the absorption of Mercury, and that there was no difference between Atoxyllic and Acetylatoxyllic Mercury as regards their toxicity.

(35) E. Lesser and (36) Mickley were the first to report clinical experiments with this drug in human Syphilis. They used the preparation in an emulsion of 1:9 olive oil and exhibited it intra-muscularly. They obtained very successful results and found that .1 gramme ($1\frac{1}{2}$ grains) was enough to cause papular syphilides to fade and papular infiltrations to subside, that after the third injection usually nothing was left of the papular rash except some pigmentation without infiltration, and that excellent results were obtained in malignant syphilis, ulcers healed and became clean in a very short time, that it had favourable effects upon the ulcerous and gummatous cutaneous lesions of tertiary syphilis. while the patients' general conditions improved, secondary effects were very slight when it was carefully used, provided that the mouth was kept in good condition and the treatment was not used in cases where there was injury to the eyes. Lambkin (37) gave a detailed description of the use of Atoxylate of Mercury in a series of thirty cases treated by him at the Military Hospital, Rochester Row. The preparation he used was manufactured by the Vereinigte Chemische Werke A.G. Charlottenburg (the manufacturers of the original Atoxyl) and supplied by Messrs Greef & Co. of London. He said, in the paper, that he had not then had one case

showing the slightest toxic effects, that all had greatly benefitted by it, that under it all the active symptoms cleared up in a marvellous way, even more rapidly than when Calomel was used.

After numerous cases treated by me with a 10% atoxylate of Mercury cream after the formula of Colonel Lambkin as given in the Lancet, January 1st, 1910, and procured from Messrs Oppenheimer Sons & Co. of London, I can say for certain that I have never in any single case observed any intolerance of the drug or any toxic symptoms. I may mention that this drug is to be given intra-muscularly (and in parts devoid of fat as much as possible) and not subcutaneously. (38)
It is interesting to note that E. Mameli and G. Ciuffo describe a mercury-para-amido-phenyl-arsinate prepared by them, to which they give the name of "aspirochyl" and that the results obtained by them with its use are claimed to be very satisfactory.

Dioxy-diamino-arseno-benzol or Ehrlich Hata "606" (also called Salvarsan), the newest and most important arylarsonate, was introduced by Ehrlich towards the close of 1909 in the treatment of Syphilis and was prepared by Dr Bertheim, Ehrlich's experienced fellow-worker. In this chapter, I shall deal as far as possible and in chronological order with the progress of this new preparation from its introduction up to the

time of delivery of this thesis. It has perhaps been more extensively used than any other arylarsonate and hence its literature is almost legion. The most important features that occurred in the earliest experiments on man were:-

- (1) Pain of varying degrees of intensity at the seat of injection.
- (2) Increase of temperature never above 38.8°C .
- (3) A modification of the Wassermann reaction.
- (4) A varying amount of leucocytosis.

In January 1910, Dr Schreiber (of the Altsäcker Hospital in Magdeburg) recorded his experience in twenty-seven cases of well-marked Syphilis, and said that the results can without hesitation be recorded as most startling. Primary sores showed marked decrease in a few days, the hardness, etc. disappearing, and that coincidence was quite out of the question for in every single case the specific influence of a single injection was quite incontestible. He observed an increase in weight among his patients and an alteration in ^{the} Wassermann reaction. The next person to record success with this drug was Professor W. Wechselmann⁽³⁹⁾ who discovered that it influenced the symptoms of Syphilis in all its protean forms with a certainty and a rapidity that no other method hitherto known can so much as approach, and that cures were so rapid that he could not demonstrate the cases, for after a

few days there was nothing more to be seen and the patients left the hospital. He found that the Wassermann reaction was modified after a few days of treatment and that some of his cases that were markedly resistant to the long continued use of Mercury and Iodide readily yielded to it. Dr Siesskind (Professor Wechselmann's assistant) found that the spirochaetae disappeared from the blood in a day, but sometimes only after several days, while on the second day they were swollen and their movements had undergone a change. Up to the time of his address on July 4th, 1910, Professor Wechselmann had not seen any cases of recurrence of the disease after treatment. He found that the injections themselves were not painful, but for days after, there was pain of varying intensity which sometimes had to be relieved by narcotics. Occasionally, there was pyrexia (varying from 38° to nearly $39^{\circ}\text{C}.$) and oedema of the parts. Professor Alt⁽⁴⁰⁾ in July 1910 reported favourably upon lecithin metabolism following its use. He announced that the excretion of arsenic did not proceed as rapidly as was maintained by others perhaps on account of the intra-gluteal injection becoming encapsulated and so its excretion being delayed. He found it especially useful in syphilitic icterus (so common in tropical countries) and in Epilepsy with a luetic taint and

recorded some slight improvement in cases of tabes dorsalis. After having tested its efficacy on 150 cases he concluded that there was never so effectual a specific remedy as the new Ehrlich preparation.

In June 1910, Professor Leonor Michaelis⁽⁴¹⁾ (Berlin) recorded its undoubted efficacy in two cases of malignant Syphilis that had resisted treatment with Iodides and Mercurials.

On June 22nd, 1910, Dr Schreiber (of Madgeburg) informed the Berlin Medical Society that he had treated 150 cases with Salvarsan both intra-muscularly and intravenously and in every case he had observed an immediate diminution in the syphilitic signs, and occasionally a copious exanthema following its use. About the same time Dr Heubner found that the symptoms disappeared more quickly with intravenous injection and that the arsenic was more rapidly excreted.

Ehrlich⁽⁴²⁾ himself in 1910 told us that the arsenic was absorbed slowly after intra-muscular injection because "a necrosis of the muscle occurs at the seat of the injection, enclosing the drug, and disappearing slowly".

Before the Royal Society of Physicians at Vienna on June 24th, 1910, Privat-Dozent Doctor Dörr said that the instantaneous results after Salvarsan were startling and improvement was observed after Mercury

and the Iodides had been tried for years and failed.

On June 30th, 1910, Professor A. Neisser⁽⁴³⁾ reported that it exerted a powerful, direct, remarkable effect on the Spirochaetes as well as on the syphilitic manifestations, and observed that both in the Syphilis of man and animals, the spirochaetae rapidly disappeared. He saw so rapid a retrogression of the primary sores, of papular syphilides, especially of ulcerative processes, and in malignant Syphilis that there could be no doubt as to the specific action of the remedy. He, however, saw recrudescence which he attributed to the dose being too small. Whenever possible, he used the intravenous injection and the only symptoms he observed were slight pyrexia and pain at the seat of injection, and on one occasion a marked leucocytosis.

⁽⁴⁴⁾
Dr Spatz's experience in a long series of cases was that the following occurred after its use.

- (1) Pain at seat of injection.
- (2) Pyrexia of varying amount but never exceeding 39.2°C.
- (3) Frequent headache, nausea and restlessness.
- (4) Urticarial-like cutaneous rashes.
- (5) Polyuria.

His experience as to the efficacy of the drug is also in accordance with those of the preceding physicians mentioned here.

The experience of Drs Jéronne⁽⁴⁵⁾ and Huggenberg in thirty-five cases was that in most of them, although the lymphatic glands remained swollen, no spirochaetae could be found the day after the injection either in the primary sore or in the secondary ulcerations. The Wassermann reaction was, however, an inconstant phenomenon.

Dr W. Pick, on June 12th, 1910, recorded before the Royal & Imperial Society of Physicians at Vienna the result of thirty-five cases he had treated, confirmed the expressed opinions that it succeeded where Mercury and the Iodides had (after fair and prolonged trial) proved useless, and that in most cases the symptoms disappeared "with greater rapidity than had ever been found with any remedy", and that with the rapid disappearance of the symptoms, there was infrequently in a few days a marked increase in weight.

On June 23rd, 1910, Professor Treupel⁽⁴⁶⁾ communicated the results of 500 cases treated till then at the Royal Institute for Experimental Therapeutics at Frankfurt-on-Main . He recommended that the drug be used when the diagnosis of Syphilis or meta-syphilis be made by the best available means, that is, the Wassermann reaction and the examination of several lumbar punctures (Nonne-Apelt method) or when recrudescences repeatedly occurred, despite mercurial treat-

ment by the most approved methods, and there was perhaps some strain of spirochaetae resistant to Mercury, and that intra-muscular injections should be employed on account of the guarantee of a prolonged action of the arsenic in view of its slower excretion. As regards the effects of the remedy, he said that the specific effect upon the syphilitic rash, papules, ulcers and mucous membranes was undeniable and that the cures were so rapid that the cases soon passed out of sight. He, however, considered that it was too early to give any reply as to the question of the duration of the cure, and that the phenomenon of the Wassermann reaction was inconstant.

Drs Boháč⁽⁴⁷⁾ and Sobotka, however, on July 25th, 1908, reported alarming symptoms following its use.

Among the symptoms recorded by them were the following:-

- (1) Retention of urine, lasting for more than half a day.
- (2) Absence of the patellar and some other reflexes.
- (3) Rectal tenesmus with obstinate constipation.

They, however, despite these symptoms, were able to confirm the views already largely expressed as to its curative power.

Several ascribed these latter alarming toxic symptoms to the methyl-alcohol which they used to

dissolve the Ehrlich-Hata preparation. They, however, deny this, and recorded cases of recurrence of syphilitic symptoms after its use.

On August 1st, 1910, Schreiber & Hoppe⁽⁴⁸⁾ recorded very quick results obtained in 120 cases that were treated by the intravenous method.

On July 31st, 1910, Hoffmann⁽⁴⁹⁾ (Bonn) reported very good results in many cases. He observed a few recurrences and warned us that with the new remedy we were "not to forget the value of increasing doses of Iodides and injections of Mercury in Malignant Syphilis".

On August 8th, 1910, Privy Councillor Professor-Doctor A. Neisser⁽⁵⁰⁾ stated that in the 2,500 cases which by then had been treated, there was only one case of really serious organic disturbance which could with certainty be attributed to the drug, the effects surpassed anything hitherto seen, even in the most striking result obtained with Mercury or the Iodides, and that lesions of primary and secondary Syphilis rapidly disappeared. The spirochaetae also rapidly disappeared while recurrences were observed in five cases which were treated with insufficient doses. He did not fear that with repeated injections the germs would become arsenic proof, advised local treatment as well, and that it should be employed where Mercury

could not be tolerated or had no effect. He was convinced that the position was so far assured that we must now advise every syphilitic, when no special contra-indications exist, to try the new remedy.

Dr Wechselmann⁽⁵¹⁾ after an experience of 503 cases said that there was almost without exception an increase in weight, and a remission of the night pains of Syphilis in bones, while recurrent cases quickly yielded to a second injection. He raised the question as to whether certain strains of spirochaetae were arsenic-proof and recorded marked amelioration of symptoms in tabes dorsalis of syphilitic origin. Ehrlich⁽⁵²⁾ had no case of blindness to record up to August 12th when 4,000 cases had been treated and said that a complete cure was possible in man in 90% of the cases.

On August 18th, 1910, Professor H. Herxheimer⁽⁵³⁾ recorded the result of extensive personal experience and endorsed all the good qualities claimed for the drug. He said that compared with Calomel injection, the verdict was in favour of arsenobenzol. He regarded heart diseases, optic nerve anomalies and bronchiectasis as contra-indications, and advised that children with congenital Syphilis should not be injected.

On August 15th, 1910, Dr H. Isaac⁽⁵⁴⁾ reported

that "there was an incomparably prompt, often rapid and complete action of the drug upon the spirochaetae and upon the re-absorption of the pathologico-anatomical changes there present".

In seventy-one cases treated by Michaelis ⁽⁵⁵⁾, he had never seen any untoward results.

Dr Heinrich Loeb ⁽⁵⁶⁾ on July 26th 1910 reported that after a single injection, we obtained the same results formerly obtainable after months of mercurial inunctions or injections.

On August 16th, 1910, Iversen ⁽⁵⁷⁾ of St. Petersburg announced that the "Ehrlich-Hata remedy could bring about the disappearance of the symptoms of Syphilis in the shortest possible time."

On August 22nd, 1910, Professor Kromayer ⁽⁵⁸⁾ in describing the results of his cases recommended the treatment by the old and newer remedies in ordinary cases, "606" alone when Mercury cannot be supported, and for the treatment of the chancre before there was any secondary symptoms.

Mr J. E. R. McDonagh ⁽⁵⁹⁾ in describing twenty cases treated by him concluded that there was no doubt that by Ehrlich's genius the greatest victory over Syphilis had been obtained. In these cases also there was general improvement in the patients' condition. On September 17th, 1910 (p.793) the corres-

pendent of the British Medical Journal at Budapest gave abstracts of a few cases published in the Gyógyaszal which showed that Ehrlich's drug acted quickly in the different stages and manifestations of Syphilis The most striking feature was that severe cases and those which did not react to mercury, quickly and surely responded to the new drug.

McDonagh ("The aetiology, treatment and pathology of Venereal Diseases as we see them to-day, with special reference to '606'" - Practitioner, November 1910) said that a new drug called dioxy-diamino-arseno-benzol was engaging everybody's attention, and that its aim was not only to cure Syphilis after one injection! but also to prevent any recurrences and that under its use lesions disappeared in a marvellous manner, while James McIntosh (Lancet, September 3rd, 1910) expressed the opinion that the new product was the outcome of painstaking research on the part of Ehrlich & Dr Bertheim, it was a substitution product of Atoxyl, it was in the highest degree parasitotrop without being organotrop, that the protozoa were destroyed before they had a chance of developing immunity to the remedy, and that marvellous results were obtained without the least ill effects.

Knuthsen⁽⁶⁰⁾ remarked that the discovery of "606" was no mere chance but was due to a series of experi-

ments scientifically and admirably carried out with scrupulous care and attention and exploited quietly and unostentatiously with care and patience by a great star and his satellites.

In the Lancet of September 3rd, 1910, Dr J. E. R. McDonagh gave a report of twenty cases treated by him with "606". He remarked that the earlier the Syphilis, the larger the dose required (.45 to .6 gramme) and that .3 gramme was ample in the late stages. He observed in every case a marked improvement for the better, that the severer the case the quicker the action of the drug, that the results so far obtained were beyond one's expectations, and that we were on the right road to find an absolute cure for a disease which is a curse to mankind.

The same author (in "Further experience with '606'", Lancet, October 22nd, 1910) recorded cases of malignant Syphilis resistant to Mercury readily yielding to the new preparation, and that after an injection, the Wassermann reaction had a tendency to become negative. He records twelve deaths (most of which occurred after the drug had been given as a last resource) in 12,000 cases that were treated.

THE CHEMISTRY OF THE ARYLARSONATES.

Arsenium is a metalloid and from its physical and chemical properties has been included along with antimony, sulphur and a few other elements in the inorganic group of chemical substances. It is polyvalent and thus is included both among triads and pentads. It also forms two classes of compounds, viz. arsenious and arsenic. Despite the fact that it is an inorganic substance, it nevertheless lends itself to the formation of organic compounds. Although itself a poison - and forming compounds with varying degrees of toxicity - its derivatives are sometimes used externally; while internally, it is extensively used in various pathological conditions. In recent times the pharmacological action of arsenic and its salts has been thoroughly worked out and the therapeutic indications of the organic salts are now well defined. Further and more recent investigations, resulting in the introduction of its organic salts, mark a great advance in the knowledge of the subject. The great interest of these organic preparations lies in the fact that much larger quantities of arsenic can be administered when given in the form of an organic salt than was formerly possible and its remedial efficiency is consequently enhanced.

Arsenic Acid or Ortho-arsenic Acid. As O(OH)_3 , it was found, could have one or more of its hydroxyl (OH) radicles replaced by an organic group with a greater or less reduction of toxicity, according to the nature and extent of the substitution.

When one of these OH or hydroxyl groups is replaced by an organic radicle (such as Methyl (CH_3)), the resulting compound is an Arsonic Acid and its salts are called arsonates. When two such groups change places, the product is an Arsinic Acid and its salts are arsinates.

An arylarsonate is an aromatic or benzene arsonate; Aryl indicating phenyl, tolyl, xylyl or naphthal, etc. as applied to substituted hydroxyl in arsenic acid. When the substituted hydroxyl belongs to the fatty or paraffin series such as methyl, ethyl, etc. the arsenic acid becomes an alkylarsonic acid and its salts are called alkylarsonates. Bearing in mind what an arylarsonate is, we find that in the case of Atoxyl and Soamin, the aryl radicle is aniline a coal-tar derivative.

I may summarise the preceding as follows:-

- (1) Arsenic Acid = As O(OH)_3 , and its salts are arsenates.
- (2) Replace one of the OH or hydroxyl groups by an organic radicle as Methyl (CH_3) and this becomes an arsonic acid, e.g.
 $\text{CH}_3 \text{ As O(OH)}_2$ = methyl-arsonic acid.

- (3) Replace two such groups and we have an arsinic acid. Thus $(\text{CH}_3)_2 \text{As O OH} =$ dimethyl arsinic (or cacodylic) acid.

From experiments carried out by Professor Fraser of Edinburgh we know that sodium cacodylate (an organic preparation of arsenic) is excreted as such and is far less toxic than inorganic arsenical salts such as sodium arsenate, etc. More recently another compound, still less toxic than the cacodylates, was produced by heating arsenic acid with aniline. This product is called Atoxyl. In this chapter, I propose to deal chemically and in the same order with the arylarsonates already mentioned in the historical section.

When Atoxyl was first discovered, it was supposed to be a direct compound of arsenic and aniline and was termed meta-arsenic anilide which name we now know to be wrong. Later on, it was called Anilarsonate which is also a misnomer as the compound contains no aniline. It is really an arsonate of Sodium - the sodium salt of an arsonic acid containing the amino-phenyl group in place of one of the OH groups.

Thus Amino-phenyl Arsonic acid is $(\text{C}_6\text{H}_4 \text{ NH}_2) \text{As O}(\text{OH})_2$ and its sodium salt is $(\text{C}_6\text{H}_4 \text{ NH}_2) \text{As O. OH ONa}$ which is the correct formula for Atoxyl or p-amino-phenyl-arsonate. Its alternative formula will be found in the table at the end of this section.

The amount of water of crystallisation is inconstant, depending upon the method of production and conditions of crystallisation thereby causing the quantity of arsenium to also vary.

Fourneau⁽¹⁾, in the substance used by him, found two molecules of water of crystallisation. Moore, Nierenstein and Todd⁽²⁾ described a product with three molecules, and Ehrlich and Bertheim⁽³⁾ a product with four molecules. This last compound constitutes commercial Atoxyl with 24.12% of Arsenium and crystallises when special measures are taken, in very refractive bold crystals. Its extensive use in trypanosomiasis and protozoal diseases has made it desirable to have a definite compound of standard strength - since the results obtained by French and German Atoxyl differ so widely - and with this end in view, elaborate investigations have been taken and various synthetic chemical compounds with various definite strengths have been used.

Chemical and Physical properties of Atoxyl.

(1) A white amorphous, crystalline or yellow powder when exposed to light.

(2) Taste refreshing, soluble in six parts of cold water and readily in boiling water, with a slightly acid reaction. Readily soluble in alcohol. Its aqueous solutions are decomposed by light and by heating.

(3) Often contains parafuchsin, aniline and inorganic arsenic as impurities.

(4) When heated, it slowly decomposes (without fusing) and gradually assumes a brown colour.

(5) On the addition of dilute acids, the free acid is precipitated in solid white flakes easily soluble in excess of mineral but not of acetic acid.

(6) Insoluble in Ether, Benzol, Chloroform and Acetone.

Tests.

A 10% aqueous solution of Atoxyl gives with

- (a) Ferrous sulphate solution an olive green precipitate.
- (b) Mercuric Chloride solution a white precipitate.
- (c) Nickel Chloride } solutions; at first a
- or } white solution, but lat-
- (d) Magnesium Sulphate } er on a crystalline pre-
- } cipitate.

Various other coloured precipitates are given with solutions of other heavy metallic salts.

The most sensitive test is the mixture of hypophosphorous and hydrochloric acids originally introduced for the detection of arsenic in glycerine, viz:-

Sodium hypophosphite	1 part
Water	1 "
Hydrochloric Acid	10 parts

By this test, the presence of .05 milligramme of Atoxyl can be demonstrated by the production of a deep brown precipitate on warming and thus we can estimate the rate and amount of the elimination of Atoxyl from the kidneys. If to the mixture of reagent and (Atoxyl) solution we add two drops of *N.* Iodine solution, we can detect .92 milligramme of arsenic acid.

SOAMIN to all intents and purposes is a pure form of Atoxyl with five instead of four molecules of water of crystallisation. Thus Amino-phenyl arsonic acid (as we have already seen) is $\text{C}_6\text{H}_4(\text{NH}_2)\text{AsO}(\text{OH})_2$ and its sodium salt is $\text{C}_6\text{H}_4(\text{NH}_2)\text{AsO}(\text{OH})(\text{ONa}) \cdot 5\text{H}_2\text{O}$ which is also the formula for Soamin. The table at the end of this section will show at a glance the further differences between it and Atoxyl.

(1) It is soluble in five parts of water at 60°F and in three parts of water at body temperature, giving a neutral solution which can be sterilized by boiling - without undergoing decomposition - for five minutes.

(2) It contains 22.8% arsenium with $1/40$ the toxicity of Arsenious acid. It is a pure and stable salt.

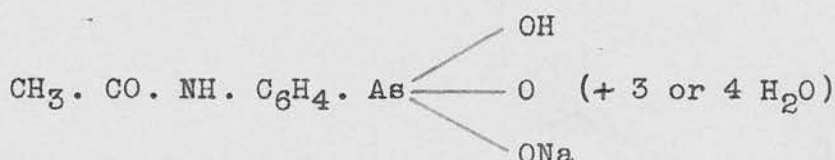
Arsacetin or Sodium Acetyl-Arsanilate.

This is derived as follows:- Para-amino-phenyl-arsonic acid is acetalysed and forms an Acetyl-para-

amino-phenyl-arsonate whose sodium salt is called Arsacetin with a formula as follows:-

This formula, according to Martindale, is
 $C_2H_3O \cdot NH \cdot C_6H_4 \cdot AsO \cdot (ONa) (OH); 5H_2O$

According to E. Merck's Annual Report, 1908, Vol. XXII. page 132, its formula is



Properties.

(1) It is a white crystalline powder, soluble in ten parts of cold water and in about three parts of hot water. It is readily soluble in Methyl Alcohol.

(2) It is absolutely free from arsenic and arsenious acid.

(3) It can be heated to $130^{\circ}C$ for an hour in an autoclave without decomposition and its solutions are unaffected by boiling.

Tests.

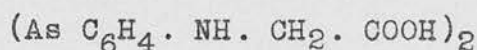
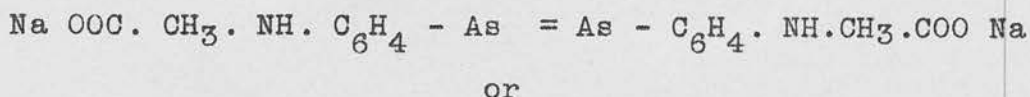
(1) 5% Solution of Arsectin + equal quantity of Liq. Sod. Hypochlor = nil.

(2) 5% Solution + equal part of Barium Chlor. Solution and strong Ammonia = dense crystalline precipitate.

(3) 5% Solution + $N/10$ of $K_2Mn_2O_4$ = Red colour, no precipitate on boiling.

ARSENO-PHENYL-GLYCIN or SPIRARSYL.

This salt has the following composition:-



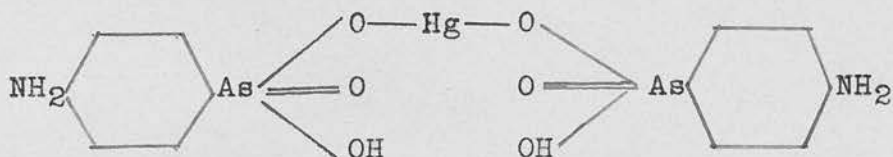
Properties.

(1) A pale yellow powder readily soluble in water.

(2) Must be kept in sealed glass tubes, the air in which has been expelled, else it is readily decomposed by the atmosphere.

MERCURY ATOXYLATE (also called Asyphil).

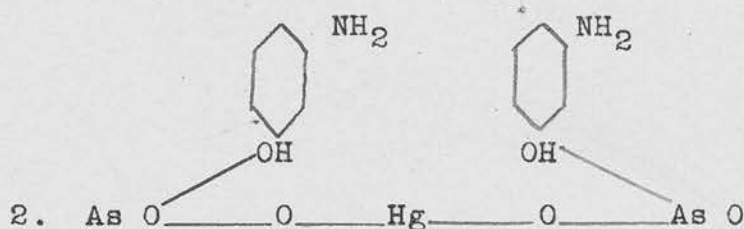
This is the mercury salt of para-amino-phenyl-arsenic acid. Various formulae are given for this preparation. According to E. Merck's Annual Report, Vol. XXII. page 142, 1908, its formula is



According to Lambkin in the Lancet of January 1st, 1910, in the article "The combined mercurial and arylarsonate treatment of Syphilis", the preparation

of Atoxyl and Mercury made for him by the Vereinigte Chemische Werke A. G. Charlottenburg was described by them (the makers) as the acid mercury salt of Atoxylic acid and having the following chemical constitution.

1. $C_{12}H_{14}O_6N_2As_2Hg$ = Empirical formula from analysis



Probable constitutional formula.

It contains 23.7% of Arsenic and 31.8 Mercury.

Properties.

(1) A white crystalline powder with no water of crystallisation.

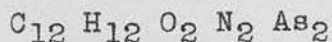
(2) Practically insoluble in water.

(3) It assumes a pinkish tinge when heated to $100^{\circ}C$.

(4) Its solution does not precipitate albumen.

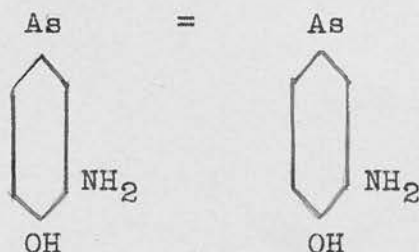
DIOXY-DIAMIDO-ARSENO-BENZOL (Salvarsan) or Ehrlich-Hata's preparation "606".

The formula for this, according to Dr Bresler is

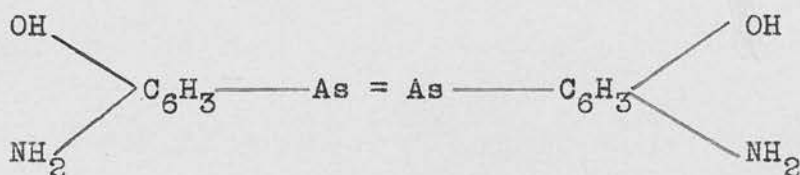


It was prepared by Dr Bertheim, Professor Ehrlich's co-worker.

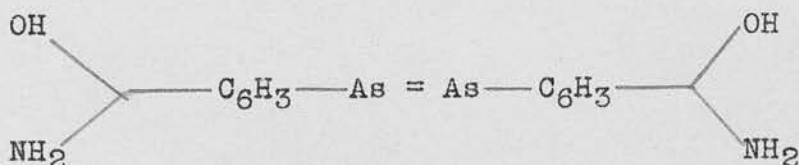
Its formula, according to McDonagh⁽⁴⁾ is graphically as follows, and it has for its basis p-oxyphenyl-
arsonic Acid which can be prepared by acting upon
Phenol with Arsenic Acid.



Knuthsen⁽⁵⁾ expresses the formula as follows:-



After being prepared for use (usually by way of
intra-muscular injections) the new formula (according
to Knuthsen) reads as follows:-



H	Na
OH	Cl

H	Na
OH	Cl

Properties.

(1) A bright yellow powder put up in hermetically

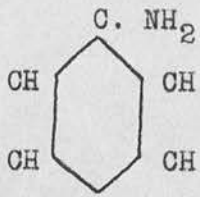
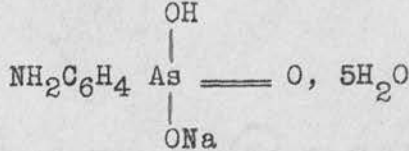
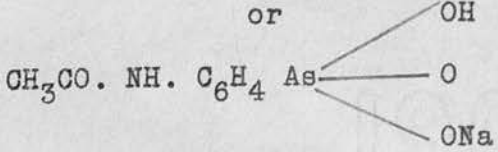
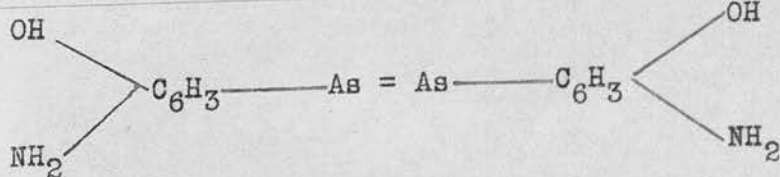
sealed bottles filled with an enert gas to prevent oxidation. It is slowly but completely soluble in water, with a strongly acid reaction.

(2) Only stable as a bichloride but since it is not to be injected in the double salt forms, it is converted into a mono- or bi-sodium salt by the addition of Sodium Hydrate just before use, which, being unstable, must invariably be employed fresh. "606" that has become discoloured - either grey or brownish - must not be used.

Resumé and table showing some of the leading features of this section at a glance.

Atoxyl, Soamin, Arsacetin and Arseno-phenyl-glycin all contain sodium.

Mercury Atoxylate and Salvarsan (Ehrlich-Hata "606") are not substances containing sodium except when the latter is prepared for injection.

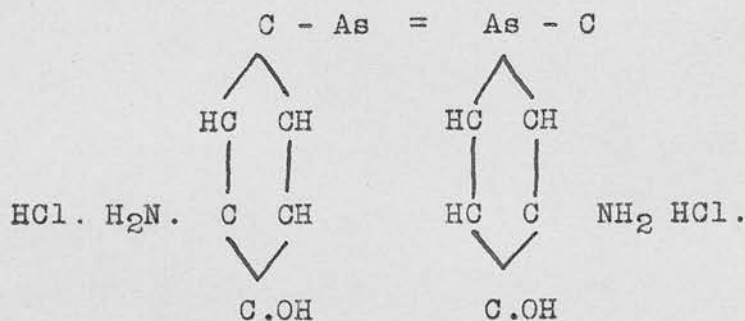
Trade Name	Chemical name	Chemical Formula	Structural or Graphic Formula.
Atoxyl	Sodium p-amino-phenylarsonate	$C_6H_7N As O_3 Na; 4H_2O$	$(C_6H_4NH_2) As O (OH) ONa + 4 H_2O$ or  $As O . OH . NaO + 4H_2O$
Soamin	Sodium para-amino-phenylarsonate	$C_6H_7N As O_3 Na, 5H_2O$	$(C_6H_4 NH_2) As O (OH)(ONa); 5H_2O$ or  $5H_2O$
Arsacetin	Sodium Acetyl-Arsanilate or Sodium p-Acetyl-Amino-phenylarsinate	$C_8H_9 N As O_4 Na$ + $5H_2O$ (Martindale) or + 3 or 4 H_2O (Merck)	$C_2H_3O . NH . C_6H_4 As O (ONa) OH \times H_2O$ or  + 3 or 4 H_2O (Merck)
Spirarsyl	Arseno-phenyl-glycin		$(NaOOC . CH_3 NH . C_6H_4 As)_2$
Asyphil	Mercury p-Amino-Phenylarsonate	$C_{12}H_{14}O_6N_2 As_2 Hg$	$(NH_2 - C_6H_4 . As O . OH . \Theta)_2 Hg$
Salvarsan or Ehrlich- Hata "606".	Dioxy-diamino-arseno-benzol	$C_{12}H_{12}O_2N_2 As_2$ (Bresler)	

The following is a table showing the Arsenic value of these preparations.

(1) Atoxyl with four molecules of water of crystallisation.	24.12% Arsenic
(2) Soamin	22.8% Arsenium
(3) Arsacetin	20.2% Arsenic
(4) Arseno-phenyl-glycin	33.28% "
(5) Mercury Atoxylate	23.7% "
	31.8% Mercury
(6) Ehrlich-Hata "606" or Salvarsan (in one form with)	40.9% Arsenic

At the commencement of this chapter, I pointed out that Arsenium was a triad as well as a pentad.

Ehrlich⁽⁶⁾ has pointed out the "parasitotropic" importance of the unsaturated trivalent Arsenic - such as we see in the formula for "606" which is according to Martindale and Westcott



The arsenic is also trivalent in Arseno-phenyl-glycin. It is, however, pentavalent in Atoxyl, Arsacetin, and some other compounds (Cacodyl).

The value of trivalent as compared with pentavalent arsenic in therapy, I shall refer to at the end of the next section of this work. To convey some idea of the laborious nature of the researches leading up to "606", it is stated that almost 200 derivatives of Phenylarsonic Acid had to be prepared, examined biologically, and tried therapeutically subsequent to Arseno-phenyl-glycin, which had the number 418, before the most active No. "606" had been synthesised.

THE PHARMACOLOGICAL ACTION AND THERAPEUTIC USES.

Before passing on to discuss in this section of my thesis the various theories as to the modes of action of the arylarsonates in vitro and in corpore and to point out their indications and contra-indications in various pathological conditions, it would be well if I were to preface it with a few general remarks on the action of drugs in protozoal diseases and to mention a few additional facts which I purposely omitted in the Chemical Section of this thesis.

Protozoa are more susceptible to the action of drugs than bacteria because they are less highly organised, are not provided with a cell-wall of much significance, and their protoplasm is for the most part motile.

Ehrlich has long since pointed out that a drug can only be of value in infectious diseases if taken up more rapidly by the parasites - "bacterio-tropous" (aetiotropus) - than by the organism ("organotropous").

As the result of numerous experiments, it appears to be proved that trypanosomes, although killed by some arsenical preparation in vitro and in corpore, acquire (a fact alleged by some and denied by others) in corpore, intolerance to the drug and this is best seen when the drug is administered by the mouth. In this latter mode of exhibition, the cells of the

alimentary canal, after a while, refuse to absorb the arsenic, so that it passes out in the faeces unabsorbed. This, therefore, means that the intestinal epithelial cells become immune to its action and it no longer reaches the trypanosomes in the blood. If, however, the drug be injected subcutaneously or intravenously, it produces its ordinary action at least for a while.

The common inorganic arsenical preparations - where the arsenic molecules seem to be rather loosely combined with the other constituents in the molecular compound - (as indicated by their relatively rapid elimination by the skin, kidneys and faeces, etc. shortly after administration which account for their relative toxicity) when compared with the arylarsonates as a group stand out in bold relief. In the latter group the arsenic radicle is in such close chemical union with the other constituents of the compound that elimination is said to begin relatively longer after administration, proceeds more slowly and is of longer duration.

Again, when the arsenic radicle in the latter group is broken up in contact with the living tissues, nascent arsenic is set free and is in a very potent chemical condition.

The phenomena of slow elimination and its com-

paratively long duration is the result of a co-operation between the living tissue and the drug and enables us to introduce far larger quantities of organic arsenic with comparative impunity when contrasted with the same element in its inorganic combinations.

I may mention here that although we may know quite well the chemistry of the arsenic body we introduce, we do not understand the protoplasmic molecule with which it is brought into contact. Furthermore, the arsenic contents (of the arylarsonates) do not necessarily act as guides to their posology.

Atoxyl was the first arylarsonate used in the treatment of Syphilis and many eminent authorities have investigated its pharmacological action, pointed out its therapeutic indications and the various morbid conditions wherein its use is to be withheld. While some consider it as a specific in Syphilis, others discard it as being useless.

Its mode of action which I shall soon indicate may be taken as representative of the other bodies in the same category. Of course, in Atoxylate of Mercury, we have a combination of the specific actions of Mercury and Atoxyl.

When first introduced into the treatment of Syphilis, Atoxyl was supposed to act simply as an internal antiseptic and was thought to kill the parasites in direct proportion to the amount of arsenic

introduced. Some experiments made in June 1907 by Breinl & Niernstein seemed to disprove this idea. In an attempt to produce an active immunity against Nagana, mixtures of atoxyl and trypanosomes were injected in different proportions, and after different periods of contact, with the idea that by increasing the amount of trypanosome-infected blood and decreasing the amount of Atoxyl, and by lessening the time of contact, a point might be reached at which virulent trypanosomes could be injected with impunity. The results obtained were not, however, what were expected. Dogs, rabbits and donkeys were used for the experiments, but invariably after the first injection, even after the exposure of the mixture for 45 minutes to a temperature of 37°C, the animals became infected after a normal incubation period. This fact seemed to suggest that the action of Atoxyl was not simply disinfectant, but was the result of a co-operation between the living tissues and the drug as already mentioned above.

Uhlenhuth, Hubner & Woith⁽¹⁾ in their experimental study on the action of Atoxyl on *T. Equiperdum* came to a similar conclusion. They state (p.296) "Unsere Meinung geht jedenfalls dahin, dass der Chemismus der Atoxylwirkung, kein zu einfacher ist, wie ihn die Theorie der Arsenspaltung supponiert,

das vielmehr beim Zustandekommen des wunderbaren therapeutischen Effektes die Körperzelle eine ganz hervorragende Rolle spielt." Their experiments were divided into two groups, the action of Atoxyl and similar compounds (Sodium arsenate, Acetylated Atoxyl, Benzoylated Atoxyl, Benzoyl-acetyl-atoxyl, Sodium-p-Hydroxy-Phenyl-Arsenate) on serum proteid being studied

(1) In vitro

(2) In vivo.

From these experiments it was made respectively clear that a combination took place between the protein and

(1) Atoxyl

(2) Mono-benzoylated Atoxyl

(3) Mono-Acetylated Atoxyl,

whilst no combination occurred respectively between these proteins and

(1) Sodium Arsenate

(2) Acetyl-benzoyl-Atoxyl

(3) Sodium-p-Hydroxy-phenyl-arsenate.

The treatment of trypanosomiasis by the above mentioned arsenical compounds also differ. Whereas, Atoxyl and Mono-acetylated Atoxyl act promptly on the parasites, the effects of sodium arsenate is less pronounced, that of Sodium-p-hydroxy-phenyl-arsenate is nil.

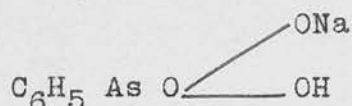
The analogy between the way in which these compounds behave with protein, and their action on trypanosomes, is very suggestive. We are, hence, led to believe that this combination with the proteins is of importance in the trypanocidal drugs, and have now to consider how Atoxyl and its derivatives become attached to the proteins.

Many protozoa we know take up dyes, e.g. Trypan Red is active against trypanosomes. Now, Ehrlich⁽²⁾ has compared the action of a drug to that of a dye. We know that it is necessary for a dye to possess a chromophoric group - a chemical radicle which causes it to be a colour - and a chromogenic group which renders it a dye. This is easily illustrated by the following examples.

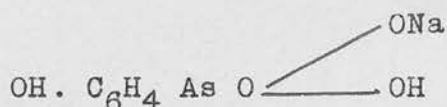
Azo-benzene ($\text{C}_6\text{H}_5\text{N} = \text{NC}_6\text{H}_5$) which contains the chromoph $\text{N} = \text{B}$, is coloured, but does not possess dyeing properties. It only becomes a dye when the chromogenic group OH or NH_2 enters.

Similarly, for example, oxyazo-benzene ($\text{OH}.\text{C}_6\text{H}_4\text{N} = \text{NC}_6\text{H}_5$) and amino-azobenzene ($\text{H}_2\text{N}.\text{C}_6\text{H}_4\text{N} = \text{NC}_6\text{H}_5$) are dyes. Their dyeing value increases with the number of chromogenic groups introduced. For this reason, tri-amino-azobenzene ($\text{NH}_2 \text{ C}_6\text{H}_5\text{N} = \text{N C}_6\text{H}_5(\text{NH}_2)_2$) is a much better dye than amino-azo-benzene.

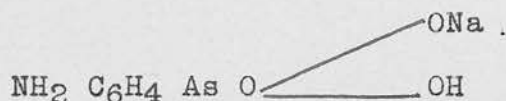
When we apply the same theory to the therapeutics of Atoxyl, we find that sodium-phenyl-arsenate



(which has been proved by Plimmer & Thompson⁽³⁾ and also in experiments conducted at the Runcorn Research Laboratory not to possess any curative effect) and also Sodium-p-hydroxy-phenyl-arsenate

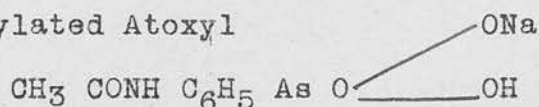


do not combine with the proteins, whilst Atoxyl

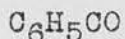
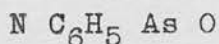
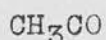


combines with the proteins and acts on trypanosomes.

Mono-acetylated Atoxyl



combines and is curative, whilst fully acetylated and benzoylated Atoxyl



does neither.

Hence we suggest that in Atoxyl the amino group and in Mono-acetylated-atoxyl^{the} amido group play the same role as the chromogenic group in a dye. It has been pointed out that the action of Atoxyl is due to

the presence of arsenic and the advantage of its use is that more arsenic could be introduced in the organism in the form of atoxyl than in the form of sodium arsenate; it might be argued from this point of view that the action of atoxyl is as follows:-

The atoxyl ($(C_6H_4 NH_2) As O \begin{array}{c} \diagup OH \\ \diagdown \end{array} ONa$) attaches itself to the proteins; the benzenes (C_6H_5) nucleus is slowly oxidised by the tissues and the arsenic is set free (in a nascent state), so that, when combined with the tissues, Atoxyl acts as a storage for effective arsenic.

This, however, is apparently not the case. It is well known that Trypan red, Afridol Blue and Afridol Violet, also Parafuchsin, have an effect on trypanosomes comparable to that of Atoxyl. These compounds do not contain arsenic, but a large number of amido groups.

Further, Laveran⁽⁴⁾ and Thomas & Breinl, have found that Sodium Arsenate in combination with Trypan red acts much better than sodium arsenate alone.

Ehrlich, in his early researches, would apparently use simultaneously a number of substances, e.g. Atoxyl, Parafuchsin, Trypan red, Trypan blue, chosen in such manner that their actions are concentrated on the parasites - whilst in the organism of the verte-

brates they are distributed over several organs - by such means he hoped to cure the disease. He suggested to combine a potent substance which will kill off the bulk of the trypanosomes with a weaker one, which will account for the few remaining ones which otherwise would certainly cause a relapse in course of time.

We have, therefore, reason to believe that the amido group in Atoxyl, and in the above mentioned colouring matters, has a specific action on trypanosomes, and that in atoxyl the effective part is not only the (nascent) arsenic but also the amido group.

In other words, Ehrlich explains the action of Atoxyl in trypanosomal diseases by the products of reduction (of the atoxyl) in the organism, and this explanation has led to the administration to the infected organism of the active reduction products of atoxyl (viz. Arseno-phenyl-glycin). How these latter compounds act will be dealt with further on in this section of the thesis. Levaditi thinks that the reduction product must first combine with albumen, to form a tox-albumen before it can act as a trypanocide but Roehl⁽⁵⁾ disagrees with this view and with that of Uhlenhuth who supposes that the parasites must first have a definite relation (though an unknown relation) to the cells of the body before they can be killed by

the substances produced by the cells of the body under the action of atoxyl.

When trypanosomes, affecting the blood of living animals, are subjected to the action of atoxyl, they are said to disappear from the blood and actually to creep through the blood vessels to escape from the arsenic only to return again when the drug is stopped. The *treponema pallidum* - the hitherto accepted cause of Syphilis - is chiefly a habitat of the blood plasma. I have, however, sometimes seen them (in specimens I have examined) in the interior of the erythrocytes, the cell walls of which were ruptured in places by the parasite - and this direct destruction of the erythrocytes may quite well account for some of the anaemia occurring in Syphilis.

In experiments carried on in rabbits which were injected with Atoxyl, it was found that the atoxyl (or its arsenical radicle) occurred chiefly in the serum and only to a very slight extent in the erythrocytes. This fact may have some bearing on its therapeutic value in some extra-corpuscular haematozoal diseases and explain the resistance of intra-corpuscular haematozoa (like the *plasmodium malariae*) to the action of atoxyl.

As stated at the beginning of this division of my thesis, some authorities think that trypanosomes (as

a class) become tolerant to arsenical preparations and that when this property is once acquired it remains as a hereditary characteristic. Ehrlich, on the other hand, thinks that trypanosomes never become tolerant to organic arsenic.

Views - quite contrary to one another - are expressed as to the value of atoxyl in Syphilis.

Can this be due to the possibility that different (as yet undifferentiated) treponemata can cause Syphilis, a disease protean in its aspects, and that some yield readily to the action of nascent arsenic eliminated during the oxidation of atoxyl in the (living) tissues, while others resist it and the amido groups mentioned above ?

Atoxyl - especially the earliest preparations used in experimental pharmacology and practical therapeutics - was an impure drug with no then definite standardization, and so gave rise to various toxic symptoms. Like other arsenical preparations it is slowly eliminated, unchanged (it is said) or in the form of some of its allied bodies chiefly by the kidneys (sometimes giving rise to albuminuria) and the bowels. Its toxic effects - when they occurred - were not due to aniline, as neither it nor p-amino-phenyl-sulphonic acid is found in the urine after its administration, but to the toxic effects of arsenic

as such (the characteristic signs of aniline poisoning being absent, and every symptom of death by arsenical poisoning being present).

The chief toxic action of atoxyl seems to be concentrated on ^{the} visual nerve apparatus. The earliest sign of this is said to be a contraction of the field of vision; while numerous cases of optic atrophy and post-bulbar neuritis (already mentioned) are authentically recorded. Its use is, therefore, contra-indicated in Syphilis affecting the optic nerves and the central nervous system (it is said).

Some authorities like Spielthoff⁽⁶⁾ regard atoxyl in full doses as a specific for Syphilis and Uhlenhuth, Sabrazès and Babesch all endorse his views.

Others, like Curschmann⁽⁷⁾ and Tomaszewski⁽⁸⁾ found that in very many cases it had no effect whatever upon the symptoms of primary and secondary syphilis.

Whatever merits are claimed for it by those who advocate its use, it certainly appears to be indicated in

- (1) Cases which prove to be refractory to Mercury after full doses of it.
- (2) Cases of so-called malignant syphilis in which the use of Mercury leads to a change for the worse in the general condition and in the specific symptoms.
- (3) In cases of patients who exhibit a marked intolerance to Mercury (administered in various ways) by the repeated occurrence of mercurial poisoning.

- (4) In cases of mercurial stomatitis when the existence of syphilitic symptoms necessitates the continuance of a specific treatment.

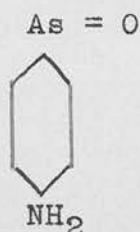
The same remarks applicable to the toxicity and other properties of Atoxyl would apply partly also to Soamin which in reality is a chemically pure form of the same drug with a definite amount of arsenic and a fixed number of molecules of water of crystallisation.

On account, then, of the occasional toxic effects of Atoxyl, various other chemical substances belonging to the same group as it were experimented with and in various ways chemically altered to decrease their toxicity. Atoxyl by then had been found out to be superior to inorganic arsenic in trypanosomiasis. It was then chemically modified and various other products were obtained, the toxicity of which was from twenty times lower to sixty times higher than that of the original product whilst the antiparasitic action on the trypanosomes was unaltered.

The most favourable results were obtained by the introduction of an acetyl radicle into the molecule analogous to the previously known favourable result of acetylation of other drugs (acetyl-salicylic acid, phenacetin-- acet-phenetidin -). These acetyl derivatives are very much less toxic and much more stable and resistant to heat than the other

derivatives which is a great advantage.

Some of the most recent investigations of Ehrlich⁽⁹⁾ are of considerable interest. He discovered that very dilute solutions of the acetyl derivative were sufficient to destroy the trypanosomes in corpore but in vitro even high concentrations (1-2%) were ineffectual. He has found the explanation of this to be in the fact that the compound was reduced in the body and that the reduced product is a much more potent trypanocide. He has produced a series of substances represented by the formulae and having the properties as indicated.

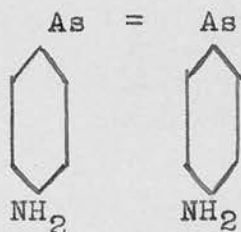


Oxidised compounds

Very toxic

Trypanocidal action in vitro weak.

and



Reduced compounds di-molecular
less toxic.

Trypanocidal action in vitro very
strong.

He then dealt in his paper with the question of the acquired resistance of the trypanosome to drugs and stated that the preparation arsenoglycin or

arsenophenyl-glycin was active when the trypanosomes had acquired resistance to the other drugs.

Atoxyl, Soamin, Arsacetin and Arseno-phenyl-glycin are chemically closely related to each other, their pharmacological actions are similar (though varying in degree) and their therapeutic indications are almost identical. The most pronounced feature, however, is their varying degrees of toxicity. Thus Soamin (practically a chemically pure and stable form of atoxyl) is far less toxic than the original atoxyl (a misnomer) and Arsacetin and Arseno-phenyl-glycin are both less toxic than atoxyl while possessing the same therapeutic action (but in greater degrees) as it. Ehrlich⁽¹⁰⁾, Browning⁽¹¹⁾ and Salmon⁽¹²⁾ formed Arsacetin three to five times less toxic than atoxyl for various animals while its trypanocidal action - as indicated above - was greater. Experiments with Arsacetin made by Ehrlich and Browning with animals (mice) infected with trypanosomiasis have proved that even the severest cases which otherwise would result in death within a few hours can be treated successfully with arsacetin, whereas Arsanilate (atoxyl) even in very slight infections, had hardly any effect.

Experiments on various other species of infected animals (trypanosomiasis as well as other protozoal diseases) have given excellent results throughout so

that the introduction of this product into therapeutics as a mode of treatment for the human being seems rational and fully justified, if any importance at all can be attached to experiments on animals. With regard to the application of arsacetin for the treatment of human Syphilis, we have accounts of experiments made by Privy Councillor Professor Doctor Neisser of the Breslau University Hospital for Skin Diseases.

At the 10th Congress of Dermatologists held on the 9th June 1908 in Frankfurt-on-Main, Neisser spoke on this subject and in his account laid down the following principles.

XVII. "In the arsenical treatment of the human being, of the products which now merit consideration, the principal one is the Acetyl compound of Atoxyl (= Arsacetin, Ehrlich). While possessing at least an equal degree of curative power, this product is much less poisonous than the original Atoxyl. Moreover, it is stable and its solutions can be sterilized by heat Apart from digestive troubles occasionally in women no other bad effects have been observed."

XVIII. "It would be wrong, however, to give up the well established treatment by Mercury in favour of Acetoxyl (= Arsacetin) - the efficiency of which

in cases of Syphilis in man is not yet sufficiently well established except in those cases where Mercury cannot be tolerated or has lost its effect (Mercury-proof spirochaetae!)."

Arseno-phenyl glycin has also been extensively used and found to be efficacious in the treatment of human Syphilis. Its elimination is slower than that of Atoxyl and Arsacetin and it is excreted by the bowels in greater quantities than is the case with the two latter preparations. Ehrlich thinks it acts on that part of the trypanosome which is concerned with multiplication.

Under its use the Wassermann reaction in most cases became negative and when not so, it was rendered appreciably less intense. In the following section of this thesis, I shall have occasion to refer to this arylarsonate.

In Mercury Atoxylate largely used in this country by Colonel Lambkin who highly recommends it (Lancet, January 1st, 1910) we have besides the specific action of this arylarsonate, the simultaneous action of Mercury one of the oldest drugs used in the treatment of human Syphilis.

The latest and without doubt the most potent preparation extant in the treatment of Syphilis in its protean aspects is Salvarsan or Ehrlich-Hata's pre-

paration "606". Its action is very rapid and it is said to have completely cured Syphilis even after one full injection! It greatly modifies the Wassermann reaction and has been very extensively used on the Continent of Europe, in England and elsewhere. As the result of this extensive use, the contributions to its literature and its therapeutic indications are very numerous. Among the peculiar phenomena observed after its use are:-

(1) The Herxheimer reaction which consists in an increased reddening and swelling of pre-existing macular and papular rashes. This reaction may be due to a direct destruction of the spirochaetae with a consequent setting free of endotoxines or to some kind of stimulus imparted to the spirochaetae with a more copious secretion of toxic matter.

(2) A leucocytosis which in some cases was very intense. In one of Neisser's cases this amounted to 38,000 which was slowly reduced.

I take this opportunity to mention that in Syphilitic affection (at all events in some of its phases) we find a leucocytosis in varying degree. In specimens of blood examined by me the mononuclear blood cells (embryonic or plasmatic cells) were much in evidence while a few polymorphs were also found.

(3) Pyrexia - where the temperature rose to 38.5° or 39°C. It may be useful to know that when we administer Salvarsan to healthy people, there is no rise of temperature observed. The pyrexia then may be due to a reaction between the endotoxines (set free by the lysis of the spirochaetae under the influence of the drug) and the infected organism.

I take this opportunity to mention that I have extensively used Atoxyl, Soamin, Mercury Atoxylate and Salvarsan and the following are some of my experiences with these various drugs.

(1) After Atoxyl injections, there was at first an exaggeration of the appearance of all syphilitic rashes and eruptions, and very often, where there was no pre-existing rash, it often produced a peculiar papular, scaly eruption of its own.

(2) Soamin, in some of my cases, gave rise to marked urticaria, headache, sickness, abdominal pain, rigors and suppression of urine which ceased as soon as the drug was discontinued, only to start again on further medication.

(3) Atoxylate of Mercury in my cases gave rise to a hard painful induration - perhaps due to encapsulation of the atoxylate cream I used and its subsequent slow absorption - which persisted for days and

even weeks at the site of the injection. There occurred also in numerous cases marked cutaneous eruptions of an urticarial type.

(4) Besides pain (of varying intensity and duration) at the seat of injection, I observed no untoward phenomena with Salvarsan.

Dr R. Sieskind⁽¹³⁾, as the result of numerous cases treated with this drug at the Virchow Hospital at Berlin, came to the conclusion that it is indicated in the following conditions:-

- (1) Cases of malignant and early ulcerative syphilis, especially those resistant to Mercury.
- (2) Cases where Mercury cannot be tolerated.
- (3) Cases where, despite full mercurial treatment, recrudescences are frequent.
- (4) Cases of primary sores before the secondary rash, preferably with the excision of the chancre or its treatment by Hollander's hot-air method, together with local injections of quite small quantities of "606".
- (5) Tuberculous syphilitics who support Mercury so badly.
- (6) Visceral Syphilis and patients with epileptiform attacks.
- (7) Decrepit persons, when the eyes, heart and lungs are sound.
- (8) Latent Syphilis, when no negative Wassermann is obtainable after treatment by Mercury and the iodides.
- (9) Parasyphilis in the first stages.

Its use is contra-indicated in

- (1) Serious non-syphilitic diseases of the retina and optic nerve.
- (2) Severe diseases of the circulatory system.
- (3) Severe diseases of the respiratory system other than tuberculosis.
- (4) Severe non-syphilitic kidney diseases.
- (5) Progressive degenerative diseases of the central nervous system.

Professor Ehrlich himself has told us that the main contra-indication is cachexia.

With regard to its use in children, Professor W. Wechselmann advises that only children with faultless nutrition should be submitted to treatment by it. He thinks it possible "that in the rapid solution of the enormous masses of spirochaetae so large a quantity of endotoxines is set free as to cause some temporary harm which the weakly organism of the child cannot overcome".

This last quotation by Professor W. Wechselmann gives us then the key to the action of Salvarsan.

Under its influence, the spirochaetae become swollen, their movements become less active and finally agglutination occurs (and in specimens I have seen, this occurs almost invariably around a leucocyte). Lysis of the micro-organisms then occurs with the setting free of enormous quantities of endotoxines which some believe are really the curative agents.

That this is so, seems to be proved by the fact that when syphilitic mothers give birth to children who show all the usual manifestations of the disease and are themselves (the mothers) injected with Salvarsan, there is a rapid retrogression of the children's symptoms when suckled by the mothers in spite of the fact that no Salvarsan is excreted by the milk. What then is curative for the infants are the endotoxines set free in the mothers' organisms and conveyed to the children by way of the breast milk.

Karl Greven⁽¹⁴⁾ of the Pharmacological Institute of the University of Bonn, has examined the question of the excretion of "606" in the urine both in men and in rabbits. His conclusions are that

- (1) The excretion commences very early (depending on the mode of introduction of the drug into the system).
- (2) The excretion is of longer duration than has hitherto been stated.
- (3) It terminates rather earlier after subcutaneous than after intramuscular injections.
- (4) Mercury given simultaneously appears to retard the excretion of arsenic in the urine, whilst iodide of potassium shortens the duration of its excretion.

When after injecting Salvarsan, a Jarish-Herxheimer reaction was found, Wechselmann considers it probable that the dose employed was too small to kill all the spirochaetae, and regards the reaction as the expression of a biological stimulus by too small a

dose. Of course a second dose can be tried, but it may give rise to symptoms of excessive reaction, or it may be useless on account of the spirochaetae becoming Salvarsan-proof! In the latter case Mercury could be subsequently employed to destroy any remaining spirochaetae.

It has been held by some observers, and to me it seems to be the case, that there are strains of Mercury-proof and arsenic-proof spirochaetae!

Many and diverse views are expressed as to the diagnostic value of the Wassermann reaction in relation to the cure of Syphilis. Some hold that a positive Wassermann reaction points to a manifest or latent syphilitic infection, others like Pick⁽¹⁵⁾ say that the Wassermann reaction is not affected by the remedy ("606"). Thus all the symptoms of the disease may disappear after injections of Salvarsan while the blood may still show a positive reaction. Neisser found after the use of Salvarsan that a negative reaction was obtained in 44% of his cases, Stern in 19.2%, Schreiber in 80% to 90%, Jérôme in 60%, while Wechselsmann in nearly 100%!

In the examination of the blood of pregnant women suffering from Syphilis, it would be well to ascertain if the Wassermann reaction is not obscured by the placental secretions! Perhaps also the exhibition

of too small a dose of Salvarsan does not modify the Wassermann reaction!

I conclude this chapter by the addition of the following table and some further reference to Arsenic as promised at the end of part three.

Preparation	Modes of Administration	Excretory Channels.	Stability	Effects on Trypanosomes.	Adult dose
Atoxyl	By mouth and locally. In fresh aqueous solutions of 5% to 15% subcutaneously, intravenously and intra-muscularly.	Principally by the kidneys and intestinal tract	Unstable: but depending on the various preparations used.	Destructive. Weak in vitro but stronger in corpore.	.5 gramme every other day for ten days. After fourteen days' interval repeat the dose if necessary and contra-indications absent.
Soamin	Ditto.	Ditto.	Stable	More destructive than Atoxyl.	10 grains of Soamin at each injection on alternate days till 100 grains are given. Repeat if necessary.
Arsacetin	Hypodermically in 10% aqueous solutions.	Ditto.	Quite stable	A rapid destruction in corpore and in vitro.	About 20 injections of 9.26 grains each. Repeat after an interval if indicated.
Arseno-phenyl-glycin	Ditto.	Largely by the bowels	Unstable. Rapidly decomposes.	Ditto.	Dose not to exceed 15 grains. To be used with caution after other arylarsonates.
Mercury Atoxylate	Intra-muscular in the form of a Creosote-Camphoric-Palmitin cream.	Chiefly by the kidneys and bowels.	Quite stable	A more rapid destructive agent than any of the preceding ones.	$\frac{3}{4}$ to $1\frac{1}{2}$ grains at certain definite periods. See Lancet, January 1st, 1910.
Salvarsan	Intravenous and Intra-muscular and subcutaneous. Also in suspension, in alkaline neutral aqueous and alcoholic solutions.	Chiefly by the bowels	Very stable	A most rapid destruction occurs in vitro and in corpore.	.4 to .8 gramme or more intra-muscularly. .4 to .6 gramme for intravenous injections

In the last part of the Chapter on the Chemistry of the Arylarsonates, I referred to trivalent and pentavalent Arsenic. Let us bear in mind that in Salvarsan and Arseno-phenyl-glycin the Arsenic is trivalent while in Atoxyl and Arsacetin it is pentavalent. Now, according to Ehrlich, pentavalent arsenical compounds should take a secondary position in spirillocide power, the reasons given being that "large doses of them are necessary, they are not very active, and further, that there is danger of optic atrophy."

The Wassermann reaction so often referred to by me is also known as the Wassermann-Neisser-Bruck blood serum diagnosis or reaction.

THE VARIOUS ARYLARSONATES DISCUSSED SERIATIM.

According to the heading of this portion of my thesis, I intend to discuss seriatim the arylarsonates already dealt with in previous chapters and to give additional information regarding their use in the treatment of human Syphilis. I propose to deal with them in the same order as before, and to arrange my discourse (whenever possible) on each arylarsonate under the following headings:-

- (1) Posology.
- (2) Methods of administration and apparatus used.
 - (a) Oral administration.
 - (b) Local application.
 - (c) Subcutaneous injection.
 - (d) Intramuscular injection.
 - (e) Intravenous injection.
 - (f) Intravenous injection followed by intramuscular injection.
- (3) Its effects on
 - (a) Primary and secondary and tertiary Syphilis.
 - (b) Hereditary Syphilis.
 - (c) Parasyphilitic lesions.
- (4) Its indications and contra-indications.
- (5) Complications occurring during or after its administration.
- (6) Phenomena occurring during its use.

- (7) Elimination of the drug.
- (8) Recurrences after treatment.
- (9) Its effects on Spirochaeta in vitro and in corpore.
- (10) Its effects on the Wassermann reaction.
- (11) Its clinical value as far as can at present be judged from clinical reports.

ATOXYL has been administered in different doses and in different physical conditions. It has been given by the mouth either alone or along with iron and quinine salts.

Alone it is given in tablet form, each containing $\frac{3}{4}$ grain of Atoxyl made up with three grains of milk sugar.

In combination with iron, it is given in two forms as follows:-

- (a) Blaud-Atoxyl Capsules, each containing $\frac{3}{4}$ grain Atoxyl and five grains Blaud's pill mass at the rate of one capsule twice daily for twelve consecutive days, then one week's pause, after which again one capsule twice daily till 50 capsules have been taken in all.
- (b) Atoxyl-Iron Tablets, each containing $\frac{3}{4}$ grain Atoxyl and $\frac{3}{4}$ grain lactate of iron. This is to be administered at the same rate as the Blaud-Atoxyl Capsules.

In combination with Quinine, it is given in the form of a capsule containing the following ingredients:-

Atoxyl 1/6 grain.
 Quinine Muriate $\frac{5}{4}$ grain.
 Strychnine Muriate 1/60 grain.
 Blaud's pill mass 5 grains.

and at the rate of one capsule three times daily.

The oral method of administration is useless because the Atoxyl is broken up by the acids in the stomach and the drug never reaches the trypanosomes in the blood.

Locally it has been applied to primary lesions in the form of a 50% ointment made up with a suitable basis.

The usual, and perhaps the only rational method of administration, is in the form of an aqueous solution varying from 5% to 10% and injected subcutaneously, intra-muscularly or intravenously. To prevent pain after injection, a 1% solution of Novocain may be added to the Atoxyl solution which must always be freshly prepared and kept in brown bottles to prevent the action of light on it. The syringe intended for use must be sterilised by dry heat or by boiling in plain water, and not in acid disinfectants which decompose the solution.

Paul Salmon uses a freshly made 10% Solution (and a quantity containing $7\frac{1}{2}$ to 12 grains of Atoxyl) thrice weekly by way of deep intra-muscular injection. It has been found to exercise a beneficial influence on all forms of primary and secondary specific lesions, while gummata rapidly disappear under its administration. It has yielded good results in cases of

Malignant Syphilis even after Mercury and the Iodides have failed. It has no influence whatever on cases of hereditary Syphilis while para- or meta-syphilitic lesions of the central nervous system are little, if at all, directly influenced by it. Its indications (already referred to in the last section of this work) are those cases where Mercury is contra-indicated, or cannot be tolerated, or has been proved wanting.

The phenomena sometimes observed in connection with its use are:-

- (1) Pain at the seat of injection (in some nervous people).
- (2) Toxic symptoms corresponding to those occurring in arsenical poisoning, viz. headache, sickness, abdominal pains, weakness in the extremities, and dark coloured urine sometimes containing blood or albumen.
- (3) Optic nerve atrophy (sometimes of sudden occurrence) and occasional post-bulbar neuritis.

Apart from these results, the effect of its administration is the causation of a rapid improvement in the symptoms. This improvement continues from day to day and the patients increase in weight. It is eliminated chiefly by the kidneys and faeces, and to a lesser extent by the saliva and skin. After its use, the disease has been known to recur on several occasions. Its effects (compared with other arylarsonates mentioned in this thesis) on spirochaetae in vitro are feeble, but in corpore it has a strong

germicidal action. Its effects on the Wassermann reaction are inconstant, and its chemical value, as far as I can gather from a careful study of a whole series of cases, is that though it sometimes succeeds where Mercury and the Iodides have failed, it is inferior to that of Arsacetin, Arseno-phenyl-glycin, Soamin, Mercury Atoxylate and Salvarsan. Its use is contra-indicated in diseases of the optic nerve and retina, and in some non-specific organic diseases of the kidneys and liver. People who are old as well as those of short stature are said not to tolerate the drug. Lambkin⁽¹⁾ thinks that it is a very weak prophylactic agent. It does not seem able, as far as one may gather from clinical reports, to sterilise the host producing Ehrlich's "Therapia Sterilisans Magna".

SOAMIN, the next on the list, has already been described as a pure and stable form of Sodium para-amino-phenylarsonate. How it differs chemically and physically from other arylarsonates, I have already mentioned. It has been given by the mouth in doses of $\frac{1}{4}$ to one grain one or two hours after food without producing toxic symptoms. The maximum daily dose for oral administration should certainly not exceed three grains, doses greater than which would cause toxic symptoms on account of their decomposition by

the stomach. It does not appear to have been locally used to influence primary lesions. Subcutaneous and intra-muscular injections are the best and most frequent modes of exhibition. The skin should be sterilized (and the same remark applies to all other injections) before its introduction, and the syringe, usually an all glass one with a platino-iridium needle, should be boiled in plain water for a suitable period before use, to render it aseptic. The usual dose for either form of injection is 10 grains dissolved in about 60 minims of boiling water. When cool enough, the solution should be drawn up into the syringe, and injected deeply into the gluteal muscles. Care must be taken that there is no hanging drop at the needle point when it is about to be plunged into the tissues, as it may cause some irritation in the track (of the needle). It should be slowly introduced into the tissues by firm continuous pressure of the piston, the syringe being completely emptied before withdrawal when an antiseptic dressing of collodion and gauze should be placed over the seat of puncture. The (intra-muscular) injection should cause no pain unless a large amount of fluid be introduced, thus causing undue stretching of the surrounding tissues and the patient should be allowed to rest a few minutes after it. For subcutaneous injections, we require

very dilute solutions (about 10 grains dissolved in not less than 120 minims of water) else very unpleasant and slightly painful indurated masses remain for several weeks after. This is, however, entirely prevented by adequate dilution. A full course of treatment by either method consists in 10 grains every alternate day till 100 grains have been administered.

The available clinical reports show that it has a beneficial influence on the disease, causing primary sores to lose their induration and rapidly heal up while enlarged glands diminish in size and finally disappear. The various secondary symptoms, such as condylomata, ulceration of the mucous membranes of the mouth, tongue and throat, skin eruptions, night pains, etc. soon disappear, while tertiary ulcers rapidly heal up. Its action on hereditary lues and parasymphilitic lesions is almost nil.

It is indicated in the following cases:-

- (1) Patients who cannot tolerate Mercury in sufficient amount to relieve their symptoms which is most often noticed in cases of extensive ulcerations of the mouth and throat.
- (2) Patients who have Syphilis complicated with tuberculosis.
- (3) Patients who for any reason cannot or will not undergo a long course of mercurial treatment.

Its principal contra-indications are in cases of diseases of the central nervous system and optic

(non-specific) nerve and retinal affections.

Sometimes, during its administration, certain undesirable effects - perhaps to be explained on an idiosyncrasy to the effects of Arsenic - are observed, the principal signs of which are visual disturbances, nausea and vomiting, gastric pain, dermatitis, nervousness and insomnia, the appearances of which are a signal for withholding the drug. Toxic symptoms are, however, very rare and it has the advantage over Mercury in not causing salivation or spongy gums. It is eliminated by the same channels as Atoxyl and cases have been known to recur after its use. Its effects on spirochaetae in corpore and in vitro and on the Wassermann reaction are about the same as those of Atoxyl. Under its use it was invariably observed that there was a rapid improvement in the patients' general health with quick retrogression of the symptoms and increase in weight. Its clinical value, then, is very great and it certainly is to be preferred to atoxyl, on account of its lesser toxicity and the rarity of ocular symptoms after its use. Some observers recommend that it should be followed, after allowing 15 to 30 days for its entire elimination from the body, by a mercurial course. The results obtained by it alone, however, are not equal to those produced by Arsacetin, Mercury Atoxylate, Arseno-

phenyl-glycin and Salvarsan.

Whether it will ultimately displace Mercury in the treatment of human Syphilis, or whether it will take a place as an adjunct or alternative to mercurial treatment, time and further clinical experience will show. What is, however, at present proved beyond doubt is that it is of great value in Syphilis and some other protozoal diseases.

Metchnikoff at the Medical Congress at Berlin in 1907, stated that with three injections of 10 grains each, he had found it, when given at the proper time, to act as a prophylactic agent in Syphilis. Lambkin, however, (Lancet, August 21st, 1909) did not observe this property in the cases that came under his notice.

ARSACETIN, the next on the list, has also been extensively used in the treatment of human Syphilis. For oral administration, its dose for adults is $\frac{3}{4}$ grain three or four times daily, and for children the same dose twice daily. Its external local use is not definitely recorded. Although given subcutaneously in sterile aqueous solutions containing $7\frac{1}{2}$ to 10 grains of the drug, it is best given in a 10% (aqueous) solution intra-muscularly and intravenously with the usual necessary antiseptic precautions, while the solutions can be boiled to render them sterile. The syringe is best sterilised by boiling in plain water

and the mode of injection is similar to that in Atoxyl and Soamin. The dose, according to Neisser⁽²⁾ is 10 grains in a sterile aqueous solution on every two consecutive days in each week until twenty injections have been given. Under its influence all active primary and secondary lesions rapidly disappear (Lambkin⁽³⁾) while tertiary symptoms are also greatly benefitted. On hereditary and para-syphilis its action is almost nil. Its contra-indications are almost identical with those of atoxyl and soamin, while its indications are the same. It is eliminated by the usual channels, but especially by the faeces and recurrences have been observed after its use. Neisser found that it has a potent parasiticide action and that apes, after its use, were incapable of conveying the infection. Its effects on the Wassermann reaction are inconstant. Besides gastric disturbances in a few cases of women to whom it was administered, Neisser found no secondary ill effects. It is preferable to Soamin and Atoxyl, as it is more stable, more potent in its action, and less toxic than either.

Lambkin⁽⁴⁾ recommends that it should be followed by a mercurial course when this is not contra-indicated, while Neisser advises us not to neglect Mercury in Syphilis until this drug has been more thoroughly investigated, and that Mercury and Arsacetin treatment

should be combined in a suitable manner. He states that he has never seen a case of optic atrophy or of similar damage to the nervous system following its use and has never observed any renal symptoms. G. Heymann⁽⁵⁾'s opinion is that this substance possesses simply a symptomatic action. Among its contra-indications already mentioned above, are to be included parenchymatous organic lesions. Of the various arylarsonates dealt with so far, the weight of clinical evidence is in favour of Arsacetin.

I end the discussion of this drug by adding that under its administration - and the same remarks apply to Atoxyl, Soamin, etc. - the condition of the fundus oculi should be constantly examined and the rate of elimination of the drug carefully noted by chemical quantitative examination chiefly of the urine and faeces.

ARSENO-PHENYL-GLYCIN, the next drug I propose to deal with, appears (when compared with Atoxyl, Soamin, Arsacetin and the newer arylarsonates) to have been very little used in the treatment of human syphilis. The one serious obstacle to its more extensive use is its ready decomposition on exposure to the air. It does not appear to have been administered by the mouth or used locally for external primary and other lesions.

Before beginning treatment by this drug, Alt⁽⁷⁾

recommends us to ascertain by means of the ophthalmic or cutaneous reaction the susceptibility of the patient to the preparation. He administers to strong persons on two consecutive days an intra-muscular injection of one gramme on each day (less robust people received .8 gramme). Of the patients treated by him, some lost the Wassermann (positive) reaction entirely while others did not lose it at all. In some, it became appreciably feebler only to return later on to its former intensity. It has no effect whatever on idiotic children with hereditary lues or on parasymphilitic conditions. Besides a slight scarlatinal rash, a slight rise of temperature, increase of pulse rate, vomiting and slight cardiac disturbances, Alt did not observe any secondary action of any moment, and in none of the cases treated by him was there injury to the Optic nerve, or albumen or sugar in the urine. In every case there was marked improvement in the patients' symptoms and general condition, and an increase of body weight. Its instability and the fact that it has to be kept in vacuo do not hold out prospects of it becoming of much use in the treatment of human Syphilis.

In ATOXYLATE OF MERCURY we have a combination of the specific action of Atoxyl and Mercury which greatly enhances its clinical value. It was intro-

duced into practical therapeutics by Uhlenhuth and Manteufel⁽⁸⁾. Though scarcely soluble in water, it possesses a specially destructive action on trypanosomes and spirochaetae which it rapidly destroys in vitro, and in this way differs from Atoxyl. It is not used by way of the mouth and for obvious reasons it is not (being insoluble in water) injected intravenously, while its subcutaneous use is not advisable. The only practical method of introduction, then, is by deep intra-muscular injection in places devoid of fat.

E. Lesser⁽⁹⁾ and Mickley⁽¹⁰⁾ use it in the form of an emulsion of 1:9 olive oil. Men receive a quantity of this (emulsion) equivalent to $\frac{3}{4}$ grains of the drug by way of intra-muscular injection, a second dose of the same amount three days later, and a third dose of 1.5 grains three days later. This latter dose is to be repeated four times at intervals of one week so that altogether the patients receive $7\frac{1}{2}$ grains of Mercury Atoxylate. The total amount administered to female patients is 7 grains, extending over a similar period.

Colonel Lambkin⁽¹¹⁾ uses it intra-muscularly in the form of a creosote, camphoric acid and palmitin cream (this cream, containing 10% Mercury Atoxylate, is supplied ready for use by Oppenheimer Son & Co. of

London) and gives it as follows:-

Hydrarg Atoxyl $3\dot{\tau}$; vehicle $3\dot{\tau}\bar{x}$

1st injection, η vii. = $\frac{3}{4}$ grain Atoxylate of Mercury

After 3 days,

2nd injection, η vii. = $\frac{3}{4}$ " " " "

After 3 days,

3rd injection, η xii. = $1\frac{1}{2}$ " " " "

After 7 days,

4th injection, η xii. = $1\frac{1}{2}$ " " " "

and so on until eight injections have been given.

Allow one month's rest and then repeat the above course.

Under its administration, infiltrations and all primary and secondary lesions rapidly disappear while in malignant Syphilis it also gives excellent results. Gummatous and ulcerative skin lesions of tertiary Syphilis soon disappear while the patients' general condition improves from day to day. Lambkin⁽¹¹⁾ says that its rapidity of action is greater than that of Calomel. The secondary effects of this drug are very slight when it is carefully used, provided that the mouth is kept in good condition and the treatment is not used where there is any injury to the eyes. Lambkin (Lancet, January 1st, 1910) observed (in his cases) no toxic symptoms and an increase in weight in every case. Although all the symptoms rapidly

disappeared, there was no alteration of the Wassermann reaction, i.e. even under treatment the reaction (as a rule) remained positive.

Albuminuria, as was to be expected, is one of the conditions under which it is inadvisable to use it.

I shall conclude this portion of my thesis by referring to Salvarsan or Ehrlich-Hata's preparation "606". It is the latest arylarsonate introduced into practical therapeutics.

Posology:

The average dose is .5 gramme for subcutaneous and intravenous injection, but larger doses up to even one gramme are advocated by the manufacturers in the case of strongly built adult males, according to the nature of the case. For women, the average dose is .45 to .5 gramme.

For very weak people .3 to .4 gramme is sufficient.

For children .2 to .3 gramme and for infants .02 up to .1 gramme.

It is not given by the mouth and has been locally applied to condylomata in the form of a 50% ointment.

Methods of Administration:

- (1) Intra-muscular Injection into the gluteal muscles.

- (2) Subcutaneous Injection into the tissues adjoining the base of the shoulder blades.
- (3) Intravenous injection. In this method which is said to be painless, the dose is given in much weaker dilution, about 200 to 250 c.c. of diluent being employed.
- (4) Intravenous followed by Intra-muscular injection to prolong or intensify the action.

Whatever its mode of introduction may be, the solutions must be freshly prepared and the skin at the seat of puncture carefully sterilised, while the syringe must be boiled in plain water. Various patterns of apparatus (modified syringes) are used for the different modes of injection.

Both the intra-muscular and subcutaneous methods of injection are apt to be followed by pain of occasionally such an intense nature that an anaesthetic — and this is usually 2 c.c. of a 1% solution of Novocain — or narcotic may be required.

The drug in the subcutaneous method is said to act more rapidly and to be more completely absorbed in comparison with the intra-muscular method.

Supplied as it is in the form of a Chloride or Bichloride with the formula $C_{12}H_{12}O_2N_2 As_2 (HCl)_2$ - with 35.15% of arsenic - and with a strongly acid reaction when dissolved in water, it must, before use, obviously be treated by an alkali to neutralise its acidity. The alkali used is $N/5$ or $N/10$ Caustic

Soda (NaHO). If rendered very slightly alkaline - almost neutral - the solubility is at its minimum; this amount of alkalinity corresponds very closely with that of the blood and tissues, and it is probable that its relatively low toxicity (in comparison with other arsenical preparations) is due to the fact that it is so insoluble in the blood. The concentration in the blood can never exceed this slight amount and Michaelis thinks that no matter in what form the substance is introduced, the solubility is never more than 1/1000 per cent.

Its effects on the various primary and secondary forms of Syphilis as indurated chancres, maculo-papular eruptions, genital ulcerative lesions, pustular and pemphigoid lesions, are marvellous. All these, and the night pains of lues, soon disappear as if by magic. It has the same effects on tertiary and other forms of the disease while its effects on hereditary Syphilis are wonderful. Para-syphilitic lesions like tabes dorsalis, progressive paralysis, etc. are said not to be influenced by it; however, even in these diseases, it should be used in their early stages.

In Syphilis complicated with other diseases as tuberculosis, its results are wonderful, while it also is of great value in severe pulmonary Syphilis. If necessary, the dose may be repeated at suitable

intervals which are said to be about four weeks. Wechselmann ("On Re-injections with Dioxy-diamino-arseno-benzol", Deutsche Med. Woch. No.37, September 5th, 1910) indeed regards a re-injection as admirable and efficacious. According to him, it may be made after eight days, but it is more effectively given three to four weeks after the first injection. If an insufficient curative dose be, however, administered at first, the "Herxheimer Reaction" (already referred to elsewhere) sometimes appears.

The arsenic is eliminated by way of the urine and faeces but at a slower rate than with Atoxyl, Arsacetin and Arseno-phenyl-glycin when injected subcutaneously. In the former two drugs mentioned here, the arsenic is excreted quickly and almost completely by the kidneys; while in the latter and in Salvarsan, it is largely found in the faeces.

There is diversity of opinion as to the recurrence of the disease after treatment by "606". Dr H. Isaac (Berlin Klin. Woch. No.33, August 15, 1910) in Lassar's Clinic at Berlin did not observe any recurrences. Others, however, have observed them but these cases are very rare and seem to have occurred mostly after the administration of insufficient doses. It is indicated in all cases of Syphilis except the following occur along with the disease:-

- (1) Severe and non-syphilitic disease of the retina and optic nerve.
- (2) Severe heart and vascular disease.
- (3) Severe pulmonary affections.
- (4) Severe non-syphilitic kidney affections.
- (5) Advanced degenerative processes of the central nervous system.
- (6) Those suffering from Angina and fever.

Its action on spirochaetae in corpore is marvelous, all disappearing from the blood in from 24 to 48 hours after injection.

The results on the Wassermann blood reaction vary and various observers record different percentages of the reaction becoming and remaining negative after an injection. Its clinical value as far as can be judged from clinical reports can be summarised as follows:-

"Arseno-benzol is a specific in Syphilis, and exceeds all other anti-syphilitic remedies in its action. It stays all forms and stages of the disease". (Dr Sellei, Münch. Med. Wochens. No.39).

Under its action all patients increase in weight. Ehrlich says that in adequate doses it can sterilise the body, and in this direction it is interesting to note that pus removed at the site of injection where infiltration and inflammation have occurred, has always been reported as sterile.

As far then as clinical tests go, it certainly leaves in the shade Mercury, the Iodides and all other substances hitherto discovered and used in the treatment of human Syphilis.

SUMMARY AND CONCLUSIONS.

In this, the concluding portion of my work, I intend to briefly state in numerical sequence the chief points about the various arylarsonates and their relative advantage, together with some remarks as to whether they are likely to replace mercurial treatment.

(1) The chief points about ATOXYL are its varying composition, its liability to contamination during the process of manufacture, its relative toxicity and its liability to decomposition under various physical and chemical conditions. Besides, there is its injurious action on the neuro-retinal visual apparatus. There is a conflict of opinion regarding its value. Although it is able to modify primary, secondary and various tertiary specific lesions, it fails in hereditary and parasymphilitic conditions. The fact that it sometimes succeeds where Mercury and the Iodides have failed, is no reason why it should be adopted as a routine mode of treatment in human Syphilis in view of the better results obtained by some of the newer arsenical preparations. The only conditions where it is likely to replace Mercury are in the various cases - already mentioned - where that drug is contra-indicated or cannot be tolerated.

(2) SOAMIN recommends itself to us on account of its definite chemical composition, its purity and relative non-toxicity. There is a unanimity of opinion as to its beneficial effects in primary, secondary and tertiary specific lesions. Authorities are also agreed as to its failure in hereditary and parasyphilitic conditions. It certainly succeeds where Mercury and the Iodides sometimes fail or are contra-indicated. Very seldom does it give rise to toxic effects or to visual disturbances. In conditions where Mercury is contra-indicated or useless, it is likely to replace it, and again in the Tropics where on account of the debility caused by climatic and malarial conditions it cannot be given. It certainly causes an increase in weight in almost every case and acts as a tonic in tropical debility. Its advantage over Mercury is that it causes no salivation, stomatitis or spongy gums. Likewise, in moderate remedial doses, it does not cause diarrhoea, a point of great value, as compared with Mercury, in the tropics where diarrhoea is such a prevalent disease or symptom.

(3) ARSACETIN recommends itself to us on account of its purity, marked stability and the rapid manner in which it modifies all forms of the disease except hereditary and parasyphilitic ones. Compared with Soamin and Atoxyl, the weight of clinical evidence is

in its favour. It does not cause neuro-retinal ocular disturbances (like Atoxyl), is relatively non-toxic, well borne and certainly indicated where Mercury is useless or contra-indicated. When possible, it should be followed by a mercurial course, and is indicated in tropical conditions. Under its action, patients rapidly increase in weight and it acts indirectly as a tonic.

Colonel Lambkin⁽¹⁾, in speaking of this drug and Soamin, said that the good results he obtained in his cases strengthened his conviction that we had in them a secondary specific for Syphilis, at least from a preventive and remedial point of view. As regards the former, he had then under his care cases with undoubted primary specific lesions which were treated with Soamin and which were closely observed every week for ten months without developing any further sign of the disease. From the remedial point of view the good results he obtained speak for it. But as a curative agent, it is beyond us all at present to give a positive answer to this all-important question; time and clinical experience alone would enable us to do so. This could not be done until it was proved beyond doubt that arylarsonates were capable of permanently expelling the spirochaetae pallida from the system, as indicated by the patient being

rendered capable of re-infection. Neisser's successful experiments on apes from this point of view justified us in hoping for this end. Until the question as to the capability of arylarsonates bringing about a permanent cure was fully established, he would give Mercury after a course of treatment by arylarsonates. Later on, the same author⁽²⁾ in speaking of the arylarsonates, said that our present knowledge of the power of these arsenical salts over Syphilis was in a very elementary stage, but he looked forward to further experience of them and improved technique leading us to that goal in the treatment of Syphilis which had already been attained with dourine. Regarding Arsacetin, Neisser⁽³⁾ says that he has hitherto applied the mercurial and arsacetin treatment simultaneously, but perhaps they could be carried out alternately.

(4) ARSENO-PHENYL-GLYCIN has been fully dealt with elsewhere and it only remains for me to say that, despite the brilliant results which follow its administration, there is no likelihood, on account of its instability and the inconvenient form in which it is supplied, of it ever replacing Mercury, and even other arylarsonates like Soamin, Arsacetin, Atoxylate of Mercury and Salvarsan in the treatment of human Syphilis.

In reviewing the arylarsonates hitherto discussed and used before the introduction of Salvarsan and Mercury Atoxylate, Colonel Lambkin⁽⁴⁾ said that it was far too soon to express an opinion as to whether they were likely to prove of permanent benefit in Syphilis or whether they were likely to replace Mercury in the disease, but the results were encouraging. Whether they had any abortive or prophylactic effect on the future development of the disease after inoculation, he was unable to speak except to note that when given at an early date they delayed and modified considerably the secondary signs of the disease and that they had very beneficial effects on all specific mucous ulcerations. It was well established, he thought, that in the arylarsonates we had a second specific for Syphilis, the importance of which could not well be exaggerated.

(5) In MERCURY ATOXYLATE we have a very potent drug exerting both the specific actions of Atoxyl and Mercury on the spirochaetae, both in vitro and in corpore. It is far more potent than Calomel injections alone. If applied to suitable cases and care taken in its administration, it is a safe drug. Lambkin and others who have used it, prefer it to Mercury over which it has a decided advantage in the rapidity with which it controls the symptoms of the

disease. I am of opinion that this drug will certainly displace the mercurial treatment of Syphilis.

(6) SALVARSAN or Ehrlich Hata's "606" is the most potent drug hitherto discovered and applied to the treatment of human Syphilis in its protean aspects. Its stability, non-toxicity, ease of administration, rapidity of action, the fact that it does not affect the neuro-retinal visual apparatus, all speak in its favour. It is indicated in all forms of the disease viz. primary, secondary, tertiary and hereditary lues, while it has a marked effect in combating some of the symptoms occurring in parasyphilis. It has yielded marvellous results in alleviating the various crises of locomotor ataxia of specific origin. With the doses at present used, cases have been said to recur, but Professor Herxheimer⁽⁵⁾, Dr H. Isaac⁽⁶⁾ and others have never seen them. Dr Leonor Michaelis⁽⁷⁾ found that the recovery was absolute in a few days in most of his cases, while Dr Gourwitsch and S. Bormann⁽⁸⁾ selected cases which had been treated with the most powerful of mercurial methods and found that the comparison of these with Arseno-benzol proved the overwhelming value of the latter.

By way of conclusion, I may say that from a personal experience of the effects produced by Salvarsan and the reports of eminent authorities, that the drug

is absolutely superior in Syphilis to any other known drug, and that a single injection, in a suitable case, will produce results obtained only after years of treatment with Mercury. This latter drug, however, is not to be discarded because it seems to have been proved that there are strains of spirochaetae that are arsenic-proof. In the same way, there are strains that are Mercury-proof. Perhaps by using one drug after the other we may be able to destroy all these various strains and so bring about a permanent cure of the disease.

In spite of the pre-eminence of Salvarsan as the best curative and prophylactic agent hitherto discovered for Syphilis, I venture to state that the last word has not yet been spoken on the treatment of Syphilis.

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